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DRINKING WATER CRITERIA DOCUMENT FOR 1,2-DICHLOROPROPANE

Prepared for

OFFICE OF DRINKING WATER

Prepared by

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on 1,2-dichloropropane. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of 1,2-dichloropropane
- Toxicokinetics and human exposure to 1,2-dichloropropane
- Health Effects of 1,2-dichloropropane in humans and animals
- Mechanisms of toxicity of 1,2-dichloropropane
- Quantification of toxicological effects of 1,2-dichloropropane

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ADI	Acceptable daily intake
bw	Body weight
CNS	Central nervous system
HA	Health advisory
LD_{50}	Lethal dose to 50% of the population
LOAEL	Lowest-observed-adverse-effect level
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
TLV	Threshold limit value
TWA	Time-weighted average
V/V	Volume per volume

I. SUMMARY

1,2-Dichloropropane is a colorless liquid used as an insecticidal fumigant, chemical intermediate, solvent, scouring compound, spotting agent and a metal degreasing compound. It has a molecular weight of 113.0, specific gravity of 1.1593 (20/20°C), a vapor pressure of 50 mm Hg at 25°C, a boiling point of 96.6°C, a freezing point of -100.44°C and a water solubility of 2.7 g/ℓ at 20°C. This compound may undergo significant biodegradation during normal wastewater treatment but is resistant to degradation in natural surface waters. Evaporation may be the primary mode of loss of this compound from aquatic media.

Pertinent data regarding the toxicokinetic profile of 1,2-dichloropropane in humans were not located in the available literature. Data on experimental animals, however, suggest that this compound is almost completely absorbed (95%) and rapidly excreted from the tissues of rats following oral administration. The metabolic pathway for 1,2-dichloropropane involves the formation of N-acetyl-S-(2-hydroxy propyl) cysteine, the major urinary metabolite, and N-acetyl-S-(2,3-dihydroxy propyl) cysteine. The major route of elimination in mammals is by urinary excretion.

The acute oral LD_{50} for 1,2-dichloropropane reported in the literature range from ~860-5000 mg/kg for mice and dogs, respectively, with other species being intermediate in sensitivity. A dosage of 2000 mg/kg/day by gavage for 14 days was lethal to mice and rats; deaths occurred among mice but not rats at 500 or 1000 mg/kg/day. Some evidence for renal effects (redness of the renal medullae) was seen at doses of 125-2000 mg/kg/day in mice and at 2000 mg/kg/day in rats. A number of studies evaluating the

effects of acute vapor exposure to 1,2-dichloropropane reported kidney, liver and adrenal degeneration in rats and guinea pigs that received 10,400 mg/m^3 (~2200 ppm) for one or a few 7-hour exposures.

Subchronic, oral exposure of rats and mice to 1,2-dichloropropane resulted in liver congestion, hepatic fatty changes and liver necrosis in rats receiving 1000 mg/kg/day, 5 days/week for 13 weeks. Slightly depressed body weight was reported in mice treated with 500 mg/kg/day on 5 days/week for 13 weeks. Subchronic studies involving inhalation of 1,2-dichloropropane reported slight liver degeneration, renal and adrenal effects, reduced growth rates, CNS abnormalities and disruption of enzyme activities.

The effects of chronic oral exposure to 1,2-dichloropropane in rats included decreased survival, hepatic foci of clear cell change and hepatic necrosis in females treated with 250 mg/kg/day (5 days/week) and mammary gland hyperplasia in females treated with 125 mg/kg/day (5 days/week). Males that received 62 mg/kg/day (5 days/week) showed no effects. In mice given 125 or 250 mg/kg/day (5 days/week), decreased survival occurred in females, liver lesions (hepatocytomegaly and hepatic necrosis) were observed in males, and slight acanthosis of the forestomach epithelium was found in both males and females.

The principal target organ for 1,2-dichloropropane toxicity appears to be the liver. Non-neoplastic lesions identified as centrilobular necrosis have been reported in animals and in one human. Effects on the kidney, adrenal and lung have also been reported in animal studies.

1,2-Dichloropropane, administered orally, produced statistically significant increases in the incidence of liver adenomas and carcinomas in both male and female $B6C3F_1$ mice. There was also equivocal evidence of carcinogenicity in female rats as indicated by an increased incidence of adenocarcinomas in the mammary gland.

1,2-Dichloropropane elicited positive responses in reverse mutation assays with Salmonella typhimurium and in forward mutation assays with Aspergillus nidulans. It was also active in in vitro sister-chromatid exchange and chromosome aberration assays with hamster ovary cells.

1,2-Dichloropropane and trichloropropane did not act synergistically with respect to liver damage in rats, as evidenced by levels of serum enzymes. Human data that would establish the existence of subpopulations having a special sensitivity to 1,2-dichloropropane were not available. Animal data suggest considerable inter- and intraspecies differences in sensitivity to this compound, and that younger individuals may be more sensitive to 1,2-dichloropropane than adults. Agricultural and industrial workers who are occupationally exposed to 1,2-dichloropropane may be at somewhat greater risk because of their additional exposure.

The data base for the toxicity of 1,2-dichloropropane is limited consisting of a number of studies from the older literature and a draft of an NTP carcinogenicity study. Thus, due to the inadequacy of the available toxicological studies, a 1-day HA and lifetime AADIs are not recommended. An interim 10-day HA of 0.090 mg/ℓ for a 10 kg child and 0.3 mg/ℓ for a 70 kg adult.

Because there is some evidence that 1,2-dichloropropane may be carcinogenic, the dose-response data for hepatocellular adenoma and carcinoma in male mice (NTP, 1983 draft) were used to estimate (using a linearized multistage model) the concentrations of 1,2-dichloropropane in drinking water that would result in increased lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6}. The corresponding water concentrations are 5.6×10^{-2}, 5.6×10^{-3} and 5.6×10^{-4} mg/ℓ, respectively. These risk estimates are based on the results of the NTP (1983 draft) report and subject to change following the audit of the experimental data and issuance of the final report by the NTP.

II. PHYSICAL AND CHEMICAL PROPERTIES

Information and Properties

1,2-Dichloropropane is also known as propylene dichloride (BCPC, 1977). It is a colorless, stable liquid used as an insecticidal fumigant and is prepared by the chlorination of propylene. Generally, it is used as a mixture with other fumigants; the technical formulation "Dowfume EB-5" (Dow Chemical Company) is composed of 7.2% ethylene dichloride, 29.5% 1,2-dichloropropane and 63.6% carbon tetrachloride (BCPC, 1977). 1,2-Dichloropropane is also used as a chemical intermediate, lead scavenger for antiknock fluids, solvent, scouring compound, spotting agent and a metal degreasing agent (Hawley, 1977).

Structure: $ClCH_2CHClCH_3$

Molecular formula: $C_3H_6Cl_2$

Molecular weight: 113.0

Chemical Abstract Service (CAS) registry number: 78-87-5

Registry of Toxic Effects of Chemical Substances (RTECS) number: TX9625000

1,2-Dichloropropane also has a chloroform-like odor (Hawley, 1977). The chemical and physical properties of 1,2-dichloropropane are listed in Table II-1.

Fate of 1,2-Dichloropropane in Water

1,2-Dichloropropane is relatively stable in water; it will not photolyze, since there are no chromophores to absorb light at wavelengths common to the troposphere (Callahan et al., 1979). It will not biodegrade significantly in surface waters (Kawasaki, 1980), although some biodegradation may take place in sewage treatment plants (Tabak et al., 1981). It will not

TABLE II-1

Physical and Chemical Properties
of 1,2-Dichloropropane*

Property	Value
Specific gravity	1.1593 (20/20°C)
Freezing point	-100.44°C
Boiling point	96.6°C
Vapor pressure	50 mm Hg at 25°C
Refractive index	1.437 at 25°C
Solubility	2700 mg/ℓ water at 20°C; soluble in alcohol, ethyl ether
Flash point (BCPC, 1977)	21°C
Ignition Temperature	557-570°C

*Source: Torkelson and Rowe (1981).

Conversion: 1 mg/m^3 = 0.217 ppm and 1 ppm = 4.62 mg/m^3 at 25°C, 760 mm Hg

sorb significantly to biota or sediments, based on the octanol/water partition coefficient of 100 (Hansch and Leo, 1979). Some hydrolysis will occur at ambient temperatures; the hydrolysis half-life based on a hydrolysis rate constant of 7.2×10^{-4} hour^{-1} (25°C) is ~40 days (Mabey et al., 1981). In open waters, the dominant removal process is volatilization. An EXAMS model of the fate of 1,2-dichloropropane in a pond, river and two lakes yielded volatilization half-lives of 1.7-10 days (Burns et al., 1981). 1,2-Dichloropropane has been detected in the aqueous environment in industrial areas (Ohio River Valley Water Sanit. Comm., 1979, 1980; Dewalle and Chiau, 1979 Dreisch et al., 1980;).

Summary

1,2-Dichloropropane is a colorless, stable liquid used as an insecticidal fumigant, chemical intermediate, solvent, scouring compound, spotting agent and a metal degreasing compound (Hawley, 1977). It has a molecular weight of 113.0, vapor pressure of 50 mm Hg at 25°C, and a solubility of 2700 mg/ℓ water at 20°C (BCPC, 1977). This compound may undergo significant biodegradation during normal wastewater treatment with activated sludge but is resistant towards biodegradation in natural surface waters. It appears that evaporation may be the primary mode of loss of this compound from aquatic media (Chiou et al., 1980; Kawasaki 1980, Tabak et al., 1981).

III. TOXICOKINETICS

Human Data

Data regarding the absorption, distribution, metabolism or excretion of 1,2-dichloropropane in humans were not located in the available literature.

Animal Data

Absorption. Information on the absorption of 1,2-dichloropropane was not located in the available literature; however, some inferences can be made from the distribution and excretion study of Hutson et al. (1971). 1,2-Dichloro[1-^{14}C]propane (0.88 mg/rat; ~4 mg/kg) in 0.5 mℓ arachis oil was administered by gavage to adult male and female rats. Excretion of radioactivity in the urine and feces was monitored. The excretion of radioactivity in expired air was studied following similar administration of a slightly higher dose (1.07 mg/rat; ~4.8 mg/kg) to female rats. Within 96 hours, ~95% of the administered radioactivity was excreted in the urine and expired air of female rats. Absorption of the compound from the gastrointestinal tract appears to be relatively complete since only ~5% of the radioactivity was recovered from the feces. Fecal recovery may have been from biliary excretion or unabsorbed compound but was not determined in this study (Hutson et al., 1971). Male rats appeared to respond similarly but exhalation excretion data were not reported, disallowing a quantitative estimation of absorption.

Distribution and Retention. Hutson et al. (1971) studied the excretion and retention of 1,2-dichloro[1-^{14}C]propane in 6 male and 6 female rats. Each animal was administered a single dose of 0.88 mg 1,2-dichloro-[1-^{14}C]propane (~4 mg/kg) in 0.5 mℓ arachis oil and sacrificed after

4 days. Approximately 0.5% of the administered radioactivity was recovered from the gut of the animals within 96 hours, 1.6% was recovered from the skin and 3.6% was detected in the carcass. The total residual radioactivity recovered in these tissues in both male and female animals 4 days following administration was ~5.7%. The total radioactivity recovered within 96 hours in the tissues, urine, feces and expired air (see Excretion Section) of female rats accounted for 106.8% of the dose. Data for male rats were similar but measurements of radioactivity in expired air were not conducted and a total recovery value was not presented. The authors stated that 80-90% of the radioactivity was excreted within 24 hours, although data for tissue levels and expired air were not provided for this time period.

Metabolism. The metabolism of 1,2-dichloropropane has been studied in vitro by Van Dyke and Wineman (1971) using supernatant and microsomes from male rat liver. [^{36}Cl]-1,2-dichloropropane was incubated with microsomes, NADP, glucose-6-phosphate, glucose-6-phosphate dehydrogenase and the 105,000 x g supernatant fraction. In this metabolism system, 1,2-dichloropropane was enzymatically dechlorinated so that ~5.8% of the available chlorine was removed from the organic moiety within 30 minutes. Jones and Gibson (1980) further characterized the metabolism of 1,2-dichloropropane using rat liver microsomes. 1,2-Dichloropropane (10 μM) was incubated with 15,000 x g supernatant from rat liver and reduced glutathione (500 μM). After 2 hours, the thiol content of the medium was not reduced, thus, no glutathione conjugates had formed. In the same study, Sprague-Dawley rats were gavaged 20 mg/kg 1,2-dichloropropane as a solution in propane-1,2-diol each day for 4 days. N-acetyl-S-(2-hydroxypropyl) cysteine was isolated as a major urinary metabolite. The authors revealed that at

least 25-35% of a single dose of 1,2-dichloropropane was excreted as this conjugate. The proposed pathways of 1,2-dichloropropane metabolism are summarized in Figure III-1. According to the authors, 1,2-dichloropropane was dechlorinated, oxidized, and conjugated to ultimately yield N-acetyl-S-(2-hydroxypropyl) cysteine. 1,2-Epoxypropane, derived from 1-chloro-2-hydroxypropane was a proposed metabolite. This epoxide was hydrolyzed in the rat to propane-1,2-diol, a nontoxic compound which is further metabolized to lactate and CO_2. ß-Chlorolactate was identified as a minor metabolite of 1,2-dichloropropane. This compound was derived from 1-chloro-2-hydroxypropane and further oxidized to oxalate. Finally, it was established that 3-chloropropane-1,2-diol was metabolized to N-acetyl-S-(2,3-dihydroxypropyl) cysteine, probably by 2,3-epoxypropane-1-ol (Jones and Gibson, 1980).

Excretion. Twenty-four hours following the administration of 0.88 mg 1,2-dichloro[1-^{14}C]propane/rat (~4 mg/kg) by gavage in 0.5 mL arachis oil to male and female rats, ~50% of the radioactivity was excreted in the urine and 4.4% was excreted in the feces. Within 96 hours, the total amount of radioactivity recovered from the urine of animals of both sexes was ~53% of that administered. Fecal elimination accounted for ~6% of the administered radioactive dose (Hutson et al., 1971). In a second experiment, five female rats were dosed orally with 1.07 mg 1,2-dichloro-[1-^{14}C]propane/rat (~4.8 mg/rat). Within 96 hours of dosing, ~19.3% of the administered radioactivity was recovered in the expired air as [^{14}C] carbon dioxide and 23.1% was recovered as other volatile radioactivity (Hutson et al., 1971). The authors stated that a portion of the administered 1,2-dichloropropane may have been exhaled as 1,2-dichloropropane through the lungs of the rats; however, the compound did undergo metabolism as indicated by the 19.3%

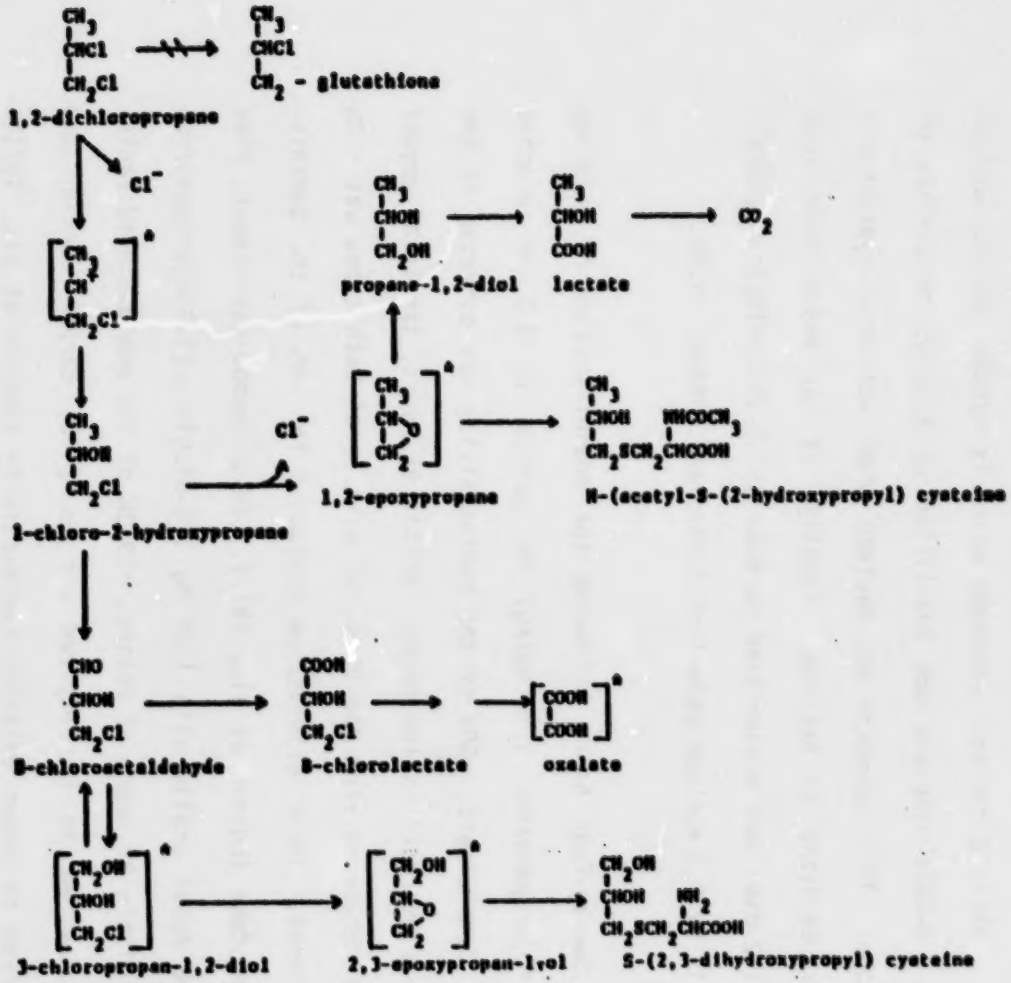

FIGURE III-1

Proposed Metabolic Pathway for 1,2-Dichloropropane in the Rat

*Compounds in brackets are proposed intermediates from Jones and Gibson (1980)

exhaled as [^{14}C] carbon dioxide. Jones and Gibson (1980) reported that at least 25-35% of a single oral dose of 1,2-dichloropropane (20 mg/kg) administered to male Sprague-Dawley rats was eliminated as N-acetyl-S-(2-hydroxypropyl) cysteine in the urine.

Summary

Although no specific data were located which quantified the absorption of 1,2-dichloropropane, it can be inferred from the study of Hutson et al. (1971) that this compound was almost completely absorbed from the gastrointestinal tract of rats. The metabolism of 1,2-dichloropropane has been studied *in vitro* and *in vivo*. [^{36}C]-1,2-Dichloropropane was dechlorinated in the presence of NADP, microsomes, and supernatant from rat liver (Van Dyke and Wineman, 1971). Upon incubation of 1,2-dichloropropane with hepatic 15,000 x g supernatant and reduced glutathione, no conjugates were formed. When Sprague-Dawley rats were dosed orally with 1,2-dichloropropane, N-acetyl-S-(2-hydroxypropyl) cysteine was isolated as a major urinary metabolite (Jones and Gibson, 1980). The proposed metabolic pathway for 1,2-dichloropropane (see Figure III-1) involves the oxidation of 1,2-dichloropropane to 1-chloro-2-hydroxypropane with ultimate production of the mercapturic acid, N-acetyl-S-(2-hydroxypropyl) cysteine. 1,2-Epoxypropane, derived from 1-chloro-2-hydroxypropane, is a proposed intermediary metabolite. Subsequently, this epoxide is hydrolyzed to propane-1,2-diol, a nontoxic compound which is further metabolized to lactate and CO_2 in the rat. β-Chlorolactate, derived from 1-chloro-2-hydroxypropane, was identified as a minor metabolite of 1,2-dichloropropane. This compound is further oxidized to oxalate. Finally, it has been suggested that 2,3-epoxypropan-1-ol is an intermediate in the metabolism from 3-chloropropan-1,2-diol to N-acetyl-S-(2,3-dihydroxypropyl) cysteine (Jones and Gibson, 1980).

1,2-Dichloro[1-^{14}C]propane was rapidly eliminated by rats dosed orally with 0.88 mg/rat (~4 mg/kg). Approximately 80-90% of the radioactivity was excreted in the urine, feces and expired air of rats within 24 hours of dosing (Hutson et al., 1971). Urinary and fecal excretion accounted for ~53% and 6%, respectively, of the radioactivity recovered after 96 hours. Approximately 19.3% of the administered radioactivity was recovered in the expired air of rats as [^{14}C]carbon dioxide; 23.1% was recovered as other volatile radioactivity, possibly as the parent compound.

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as 1,2-dichloropropane from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to 1,2-dichloropropane is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

In the Exposure Estimation Section of this chapter, available information is presented on the range of human exposure and intake for 1,2-dichloropropane from drinking water, food and ambient air for the 70 kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary Section of this chapter provides some insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. The only national scale Federal survey that included 1,2-dichloropropane as an analyte was the Groundwater Supply Survey (GWSS)

(U.S. EPA, 1983). Conducted between December 1980 and December 1981, the GWSS involved the sampling of 945 water supply systems. Approximately half of the supplies were selected randomly while the remainder were chosen by the states as having a high potential for contamination. In the randomly selected sample, 1,2-dichloropropane was observed in 6 of 466 systems (1.3%); the quantitation limit was 0.2 µg/ℓ. One of the six positive values obtained came from a supply serving fewer than 10,000 persons; the positive value was of 0.75 µg/ℓ. The other five positive values, found in supplies serving greater than 10,000 people, ranged from 0.48-21 µg/ℓ, with a median value of 0.86 µg/ℓ. In the nonrandom portion of the GWSS, 1,2-dichloropropane was detected in 7 of 479 systems sampled (1.5%). Three positives were from systems serving fewer than 10,000 people, and had values of 0.51, 1.2 and 1.4 µg/ℓ. The four positive values from supplies serving more than 10,000 people ranged from 0.21-18 µg/ℓ, with a median value of 0.7 µg/ℓ.

The levels of 1,2-dichloropropane observed in drinking water when it has been found are in the very low µg/ℓ range. Assuming that 1,2-dichloropropane is present at the highest concentration reported, i.e., 21 µg/ℓ in the GWSS, the daily intake for the 70 kg adult male consuming 2 ℓ/day of drinking water would be 42 µg/day or 0.6 µg/kg/day.

Diet. No information was obtained on the occurrence of 1,2-dichloropropane in food. Consequently, dietary intake and the contribution of dietary intake to total exposure could not be evaluated.

In the absence of adequate data, it is assumed that food is not a significant source of 1,2-dichloropropane.

Air. Brodzinsky and Singh (1982) have compiled available published and unpublished atmospheric data on 1,2-dichloropropane into a master file, and have subjected these data to statistical analysis. An assessment of the quality, reliability and representativeness of the data was also performed. Each data point was given a "quality code" based on either a quantitative assessment or on the authors' own experience and judgment. Quality codes were: 1 = Excellent; 2 = Good; 3 = Acceptable; 4 = Questionable; and Z = Unable to assign quality.

Using data for quality codes 1-3, Brodzinsky and Singh (1982) calculated the following median concentrations of 1,2-dichloropropane: urban/suburban areas, 0.26 μg/m³ (396 observations); and source dominated areas, 0.55 μg/m³ (26 observations). No data were available for rural/remote areas. The highest level of 1,2-dichloropropane measured, which was found in a source dominated location, was 0.6 μg/m³ (Pellizzari et al., 1979).

The daily respiratory intake of 1,2-dichloropropane from air was estimated using the assumptions presented in Table IV-1 and the median and maximum levels for 1,2-dichloropropane reported above. The estimates in Table IV-1 indicated that the daily 1,2-dichloropropane intake from air for adults exposed to the median levels ranges from 6.0-12.7 μg/day (0.085-0.18 μg/kg/day). In contrast, the intake calculated using the maximum level reported is approximately 14 μg/day (0.20 μg/kg/day). The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

TABLE IV-1

Estimated Respiratory Intake of 1,2-Dichloropropane

Location	Exposure ($\mu g/m^3$)	Intake	
		(μg/day)	(μg/kg/day)
Rural/remote	NA	NA	NA
Urban/suburban	0.26	6.0	0.085
Source dominated	0.55	12.7	0.18
Maximum	0.6	14	0.20

NA = Not available

Assumptions: 70 kg man, 23 m^3 of air inhaled /day (ICRP, 1975)

Summary

Table IV-2 presents a general view of the total amount of 1,2-dichloropropane received by a 70 kg adult male from ambient air, food and drinking water. Three separate exposure levels in air, four separate exposure levels in drinking water, and one exposure level from foods are shown in the table.

The data presented have been selected from an infinite number of possible combinations of concentrations for the three sources. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to 1,2-dichloropropane at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The drinking water levels selected are representative of the range of levels observed in the Groundwater Supply Survey. It is assumed that the 70 kg adult male consumes 2 ℓ/day of drinking water.

There is no information available on the presence of 1,2-dichloropropane in food; it is assumed here that food does not contribute to the daily intake of 1,2-dichloropropane.

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of 1,2-dichloropropane of 0.26 μg/m³ based on air monitoring data. Assuming an air level of 0.26 μg/m³ and the estimated 1,2-dichloropropane intake of 0 μg/kg/day from foods, drinking water would be the predominant source of 1,2-dichloropropane exposure in the adult male only at

TABLE IV-2

Estimated Intake of 1,2-Dichloropropane from the Environment
by Adult Males in µg/kg/day

Concentration in Drinking Water (µg/ℓ)	Estimated total intake in µg/kg/day (% from drinking water) based on air levels of:		
	Urban/Suburban (0.26 µg/m³)	Source Dominated (0.55 µg/m³)	Maximum (0.6 µg/m³)
0.0	0.09 (0%)	0.18 (0%)	0.20 (0%)
0.5	0.1 (14%)	0.19 (7%)	0.21 (7%)
5.0	0.23 (61%)	0.32 (44%)	0.34 (41%)
20	0.66 (86%)	0.75 (76%)	0.77 (74%)

Intake from each source:

Water: 0.5 µg/ℓ: 0.014 µg/kg/day
5.0 µg/ℓ: 0.14 µg/kg/day
20 µg/ℓ: 0.57 µg/kg/day

Air: 0.26 µg/m³: 0.085 µg/kg/day
0.55 µg/m³: 0.18 µg/kg/day
0.6 µg/m³: 0.20 µg/kg/day

Food: 0 µg/kg/day

drinking water levels above 3 µg/ℓ. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of 1,2-dichloropropane in drinking water and low concentrations of 1,2-dichloropropane in ambient air and food are unknown.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for 1,2-dichloropropane by rate of exposure. The relative dose received may vary from the relative intake. In addition, the relative effects of the chemical on the body may vary by different routes of exposure.

References

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V. HEALTH EFFECTS IN ANIMALS

Acute and Short-Term Toxicity. Lethal oral doses of 1,2-dichloropropane are presented in Table V-1. Single dose oral LD_{50} values of 860, 2200 and 2000 mg/kg bw have been reported for mice (Merck Index, 1976), male rats (Smyth et al., 1969) and guinea pigs (Farm Chemicals Handbook, 1980), respectively. A single dose oral LD_{50} of 5000 mg/kg bw has been reported for dogs (Union Carbide Co., 1960), indicating that this species is less sensitive than rodents.

In a range-finding study that was conducted as part of an NTP carcinogenesis bioassay, groups of 5 F344/N rats and 5 $B6C3F_1$ mice of each sex were administered reagent grade 1,2-dichloropropane (~99.4% pure) in corn oil by gavage at doses of 0, 125, 250, 500, 1000 or 2000 mg/kg bw/day for 14 consecutive days followed by 1 day of observation (see Table V-1; NTP, 1983 draft). The rats and mice were ~6 weeks old at the beginning of the study; necropsies were performed on all animals; however, histopathological examinations were not conducted on any of the tissues.

All of the high-dose (2000 mg/kg bw) rats died during the study, and the mean terminal body weights were reduced in the 500 and 1000 mg/kg bw male (14%) and 1000 mg/kg bw female (15%) groups (NTP, 1983 draft). Renal medullae were found to be red in 4 of 5 males and 5 of 5 females that were administered 2000 mg/kg bw 1,2-dichloropropane, but this effect was not found in rats that received lower (nonlethal) doses. In the mouse study all males at the 1000 and 2000 mg/kg bw dose levels and all females at 2000 mg/kg bw died, and 3 of 5 males at 500 mg/kg bw and 4 of 5 females at 1000 mg/kg bw also died. The mean terminal body weights of the surviving treated

TABLE V-1

Acute and Short-Term Toxic Effects of 1,2-Dichloropropane

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/Wistar	male/5	90-120 g/ 4-5 weeks	NR	gavage/NR	2200 mg/kg	single dose	LD_{50}	Smyth et al., 1969
Rat/F344/N	male/5	~114 g/ 6 weeks	~99.4%[a]	gavage/ corn oil	0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	14 days	100% mortality for males and females at 2000 mg/kg dose level; terminal body weight decreased 14% in 1000 and 500 mg/kg males, 10% in 250 and 125 mg/kg males, and 15, 8, 5 and 2% in 1000, 500, 250 and 125 mg/kg females, respectively, relative to controls; renal medullae were red in 4/5 males and 5/5 females receiving 2000 mg/kg; histopathological examinations were not conducted.	NTP, 1983 draft
	female/5	~96 g/6 weeks	~99.4%[a]	gavage/ corn oil	0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	14 days		
Rat/Sprague-Dawley	NR/39	150-200 g/NR	NR	inhalation/NR	2200 ppm (~10,400 mg/m³)	4 or 7 hours (single exposure)	No significant changes in livers of rats exposed 4 hours; some degeneration of the liver, kidney and adrenals in rats exposed for 7 hours; hemosiderin was seen in the spleen of rats exposed for 7 hours.	Highman and Heppel, 1946
Rat/Sprague-Dawley	NR/5-6 (each exposure duration)	150-200 g/NR	NR	inhalation/NR	2200 ppm (~10,400 mg/m³)	7 hours/day for 2-5 exposures	Rats killed after 2 exposures showed marked diffuse fatty degeneration of the liver and centrilobular necrosis; rats killed after 3 exposures showed advanced necrosis and fatty degeneration bordering necrotic area; rats killed after 4 exposures showed a narrow centrilobular cellular zone composed chiefly of monocytes with few necrotic cells and surrounded by a narrow zone of fatty generation; rats killed after 5 exposures showed either no change or few centrilobular lymphoid cells and monocytes with a few marginal fat-laden liver cells; some renal fat was seen in rats exposed 2, 3 or 4 times, but not in rats exposed 5 times; adrenal cortex fat was reduced after 2 and 3 exposures; hemosiderin was seen in the spleen of rats exposed 4 or 5 times.	Highman and Heppel, 1946

TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/NR	NR/20	NR/NR	reagent grade[a]	inhalation/NA	10,400 mg/m³ (2200 ppm)	7 hours/day, 5 days/week for 5-8 exposures	Gross incoordination, crusting around the nose, rough fur, coarse breathing; 5/20 died after 5 exposures; 3/8 died after 8 exposures; visceral congestion, coagulation necrosis of liver with slight centrilobular fatty degeneration; lipoid depletion of the adrenal cortex; splenic hemosiderosis only significant effect 2-4 weeks following exposure.	Heppel et al., 1946
Rat/Albino	NR	NR/NR	NR	inhalation/NA	2000 ppm (~9240 mg/m³)	8 hours (single exposure)	3/6 died	Smyth et al., 1969
Rat/NR	NR/12	NR/NR	reagent grade[a]	inhalation/NA	6900 mg/m³ (~1600 ppm)	7 hours (single exposure)	3/12 died; mild incoordination at end of exposure only sign of intoxication; histopathological examination not performed.	Heppel et al., 1946
Rat/NR	NR/13	NR/NR	reagent grade[a]	inhalation/NA	6900 mg/m³ (~1600 ppm)	7 hours/day for 5 exposures	No deaths; weight loss that was regained after conclusion of exposure; histopathological examinations not performed.	Heppel et al., 1946
Rat/CD-1	male/NR	200-250 g	>99%	inhalation/NA	1000 ppm (~4620 mg/m³)	4 hours (single exposure)	No change in serum glucose-6-phosphatase level; significant increase in SGOT, SGPT and OCT activities 24 and 48 hours after exposure.	Drew et al., 1978

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TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/white	male/NR	200-240 g/NR	NR	inhalation/NA	1000 or 2000 mg/m³ (~216 or 433 ppm, respectively)	7 days, continuous	Histostructural damage to the liver, reduced hepatic enzymic activity, reduction in content of ribonucleoproteins in centrilobular sections accompanied by microcirculatory disturbances and increased vascular permeability; hyperplasia and hypertrophy of peripheral sections of lobules; increase in number of unicellular polypoidal hepatocytes; histostructural changes in the kidney with suppression of oxidation enzymes and phosphomonoesterases; unspecified changes in blood catalase and cholinesterase activities; no effect on blood cell count, hemoglobin or body weight; results inadequately reported.	Sidorenko et al., 1976
Rat/NR	NR/NR	NR/NR	NR	inhalation/NA	1 or 2 mg/m³ (~0.22 or 0.43 ppm, respectively)	7 days, continuous	Extensive hemorrhages in lungs with desquamation and destruction of bronchial, bronchiolar and alveolar epithelium; swollen and vacuolized endothelium of arteriole and venulae; hypertrophied muscular wall; inhibition of ATPase, acid phosphatase and alkaline phosphatase in lung parenchyma and bronchi; Russian study reported as an abstract.	Bonashevskaya, et al., 1978
Mouse/NR	NR/NR	NR/NR	NR	oral/NR	860 mg/kg	single dose	LD_{50}	Merck, 1976

TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Mouse/B6C3F1	male/5	~22 g/6 weeks	~99.4%[a]	gavage/ corn oil	0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	14 days	All male mice at 1000 or 2000 mg/kg dose level and all female mice at 2000 mg/kg dose level died; 3/5 males at 500 mg/kg dose level and 4/5 females at 1000 mg/kg dose level died; terminal body weights were not affected adversely but were slightly higher than body weights of controls; renal medullae were red in all mice receiving 2000 mg/kg, in 3/5 males receiving 500 mg/kg, in 3/5 females receiving 1000 mg/kg and in 1/5 females in each of the 125, 250 and 500 mg/kg groups; histopathological examinations were not conducted.	NTP, 1983 draft
	female/5	~18 g/6 weeks	~99.4%[a]	gavage/ corn oil	0, 125, 250, 500, 1000 or 2000 mg/kg bw/day	14 days		
Mouse/NR	NR/11	NR/NR	reagent grade[a]	inhalation/NA	10,400 mg/m³ (~2200 ppm)	7 hours (single exposure)	Excitation; hyperactivity; gross incoordination; 100% mortality; histological examinations not performed.	Heppel et al., 1946
Mouse/NR	NR/10	NR	NR	inhalation/NA	6500 mg/m³ (~1500 ppm)	2 hours	3/10 died with fatty degeneration, centrilobular congestion and necrosis of the liver.	Heppel et al., 1946
	NR/22	NR	NR	inhalation/NA	6500 mg/m³ (~1500 ppm)	4 hours	22/22 died	
Mouse/NR	NR/81	NR/NR	NR	inhalation/NA	4400 mg/m³ (~1000 ppm)	0-4 hours	Mortality after 1, 2, 2.5, 3 and 4 hours of exposure was 0/11, 1/11, 3/22, 8/11 and 26/26, respectively. Fatty degeneration and centrilobular congestion of liver and slight fatty degeneration of kidney in 6/6 and 3/6 examined, respectively.	Heppel et al., 1946
Mouse/C57	NR/16	NR	NR	inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 1-12 exposures	Mortality with liver and kidney histologic damage as detailed in the Subchronic Toxicity Section and Table V-2.	Heppel et al., 1948

TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Mouse/NR	NR/NR	NR/NR	NR	inhalation/NA	26.0, 22.0, 17.5, 12.6 or 4.8 mg/L	single exposure, duration not stated	General agitation, decreased coordination, sluggishness, amyotonia, sporadic clonic spasms, loss of righting reflex; onset of effects reportedly dose-related; inadequately reported results.	Sidorenko et al., 1976
Guinea pig/ NR	NR/NR	NR/NR	NR	oral/NR	2000 mg/kg	single dose	LD_{50}	Farm Chemicals Handbook, 1980
Guinea pig/ NR	NR/39	600-800 g/NR	NR	inhalation/NA	2200 ppm (~10,400 mg/m³)	4 or 7 hours (single exposure)	Fatty degeneration of the liver and kidneys; extensive coagulation and focal hemorrhagic necrosis of the adrenal cortex; congestion with hemorrhage and parenchymatous degeneration of the adrenal medulla.	Highman and Heppel, 1946
Guinea pig/ NR	NR/4-5 (each exposure duration)	600-800 g/NR	NR	inhalation/NA	2200 ppm (~10,400 mg/m³)	7 hours/day for 2-4 exposures	Effects similar to single 2200 ppm exposure.	Highman and Heppel, 1946
Guinea pig/ NR	NR/16	NR/NR	reagent grade[a]	inhalation/NR	2200 ppm (~10,400 mg/m³)	7 hours/day for 5 exposures	Lacrimation followed by conjunctival swelling; weight loss; rough fur; coarse breathing; 11/16 died by 5th exposure; fatty degeneration of the liver (with some centrilobular necrosis) and kidneys; necrosis of adrenal cortex; some splenic hemosiderosis and pulmonary congestion.	Heppel et al., 1946
Guinea pig/ NR	NR/6	NR/NR	reagent grade[a]	inhalation/NR	6900 mg/m³ (~1600 ppm)	7 hours (single exposure)	No signs of intoxication; histological examinations not conducted.	Heppel et al., 1946
Guinea pig/ NR	NR/10	NR/NR	reagent grade[a]	inhalation/NR	6900 mg/m³ (~1600 ppm)	7 hours/day for 5 exposures	Weight loss that was regained after exposure; no mortality.	Heppel et al., 1946
Rabbit/NR	NR/4	NR/NR	NR	inhalation/NA	10,400 mg/m³ (~2200 ppm)	7 hours/day, 5 days/week for 5-8 exposures	2 died after 2nd exposure; evidence of degenerative changes in the liver and kidney.	Heppel et al., 1946

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TABLE V-1 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rabbit/NR	NR/2	NR/NR	reagent grade*	inhalation/NA	6900 mg/m³ (~1600 ppm)	7 hours (single exposure)	No signs of intoxication.	Heppel et al., 1946
Rabbit/NR	NR/2	NR/NR	reagent grade*	inhalation/NA	~1600 ppm (6900 mg/m³)	7 hours/day, for 5 exposures	No signs of intoxication; 1 rabbit was histologically examined and showed evidence of focal interstitial pneumonitis, splenic hemosiderosis and slight fatty degeneration of liver and kidney.	Heppel et al., 1946
Rabbit/ Albino	male/4	2.5-3.5 kg/NR	NR	dermal/NR	1000 mg/kg	single dose	LD_{50}	Smyth et al., 1969
Dog/NR	NR/11	NR/NR	NR	gavage/NR	0.2-0.5 mL/kg (~230-580 mg/kg)	single dose	Signs of central nervous system toxicity, histopathologic effects primarily in the liver (congestion, hemorrhage, slight cloudy swelling and fatty degeneration); other effects in the kidney (congestion), GI tract (hemorrhage, irritation) and lung (congestion, hemorrhage).	Wright and Schaffer, 1932
Dog/NR	NR/2	NR/NR	NR	gavage/NR	3 or 5 mL/kg (~3480 or 5797 mg/kg)	single dose	Dog dosed with 5797 mg/kg died with severe congestion in the liver, kidney and lungs. 3480 mg/kg not lethal to other dog, but histological examination not conducted.	Wright and Schaffer, 1932

*Reagent grade 1,2-dichloropropane that contained 0.24% toluene

NA - Not applicable; NR - Not reported

mice were not adversely affected, but rather were slightly higher than terminal body weights of the controls. At necropsy renal medullae were red in all mice of both sexes at 2000 mg/kg bw, in 3 of 5 males at 500 mg/kg bw, in 3 of 5 females at 1000 mg/kg bw, and in 1 of 5 females in each of the 125, 250 and 500 mg/kg bw groups. Treatment-related pathologic effects other than red renal medullae were not noted in the rats and mice, but again histopathologic examinations were not performed.

In an early report which evaluated the antihelmintic properties of different chlorinated hydrocarbons, dogs were orally treated with 1,2-dichloropropane (Wright and Schaffer, 1932). Eleven dogs (strain and sex not specified) were given single doses of 0.2-0.5 mL 1,2-dichloropropane/kg bw (230-580 mg/kg bw) by stomach tube and examined for gross pathologic effects after 3-4 days; microscopic examinations of the liver and kidneys were conducted on 5 of the 11 dogs. Signs of intoxication were indicative of CNS effects and included incoordination, loss of balance, unsteady gait and glazed eyes. Gross and microscopic pathological changes in the liver (e.g., congestion, hemorrhage, slight cloudy swelling and fatty degeneration) were evident in all of the dogs. Renal effects (e.g., congestion, gross discoloration) were found in 4/11 dogs and appeared to be more pronounced at the high-dose (cloudy swelling and fatty infiltration described in 1/2 dogs administered 580 mg/kg bw). Local effects on the gastrointestinal tract (e.g., hemorrhage, irritation) were apparent in 6/11 treated dogs. Oral administration of 3.0 mL/kg bw (~3480 mg/kg bw) 1,2-dichloropropane to one dog did not produce signs of intoxication, but similar administration of 5.0 mL/kg bw (~5797 mg/kg bw) to another dog was fatal; severe congestion was observed in the liver, kidney and lungs of the dog dosed with 5797 mg/kg; a necropsy was not performed on the dog exposed to 3480 mg/kg bw.

Inhalation of concentrated vapor of 1,2-dichloropropane (level undetermined) for 10 minutes was the maximum exposure at which no deaths occurred among exposed rats (Smyth et al., 1969). An 8-hour exposure to 2000 ppm (~9240 mg/m³) dichloropropane caused 50% mortality (3/6) among exposed rats (strain not specified) (Smyth et al., 1969). Of 20 rats exposed to 10,400 mg/m³ (~2200 ppm) 1,2-dichloropropane, 5 died after 5 daily 7-hour exposures and 8 died after 8 exposures (Heppel et al., 1946); mortality on days 6 and 7 of exposure was not explicated, but total mortality was apparently 15/20. Significant histological effects were not observed in Sprague-Dawley rats that were exposed to 2200 ppm for 4 hours, but some degenerative changes were noted in the liver, kidney and adrenals of rats exposed for 7 hours (Highman and Heppel, 1946). Repeated daily exposure to 2200 ppm 1,2-dichloropropane (7 hours/day, 5 days/week) produced marked degenerative changes in these organs after 2-8 exposures (Highman and Heppel, 1946; Heppel et al., 1946) (see Table V-1). Signs of intoxication included gross incoordination, crusting around the nose, coarse breathing and roughening of the fur (Heppel et al., 1946). Heppel et al. (1946) also reported that no mortality occurred among 13 rats (strain not specified) exposed to 6900 mg/m³ (~1600 ppm) 1,2-dichloropropane for 5 consecutive 7-hour exposures; weight loss was noted but necropsies were not performed. In an inhalation study with male CD-1 rats, Drew et al. (1978) determined that serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and ornithine carbamyl transferase (OCT) activities were increased after a single 4-hour exposure to 1000 ppm (4620 mg/m³) 1,2-dichloropropane, but no change in glucose-6-phosphatase was found.

Sidorenko et al. (1976) exposed an unspecified number of white male rats to 1000 or 2000 mg/m³ (~216 or 432 ppm, respectively) 1,2-dichloropropane by inhalation continuously for 7 days (see Table V-1). A number of inadequately described effects were reported in the liver (histostructural and vascular damage, reduced enzyme activities and reduced ribonucleoprotein content in the centrilobular portion, hyperplasia and hypertrophy in the peripheral portion and increased number of polyploidal hepatocytes) and kidneys (histostructural damage, reduced activity of oxidation enzymes and phosphomonoesterase). Unspecified changes in blood catalase and cholinesterase activities were also reported, but blood cell count, hemoglobin content and body weights were apparently not altered by treatment. In an English abstract of a Soviet study (Bonashevskaya et al., 1978), rats were exposed by inhalation to 1 or 2 mg/m³ (2.2 or 4.3 ppm) 1,2-dichloropropane for 7 days (presumed continuous). Extensive pulmonary effects were reported that included hemorrhage and destruction of bronchial, bronchiolar and alveolar epithelium, swollen and vacuolized endothelium of pulmonary arterioles and venules, and reduced ATPase, acid phosphatase and alkaline phosphatase levels. It should be emphasized, however, that the design and results of the above studies were inadequately reported, and that additional data were not available.

Mice appear to be more sensitive than rats with 100% mortality reported following exposure to 4400-10,400 mg/m³ (~1000-2200 ppm) 1,2-dichloropropane for 4-7 hours (Heppel et al., 1946) (see Table V-1). Mortality among mice exposed to 1000 ppm for 1, 2, 2.5, 3 or 4 hours was 0/11, 1/11, 3/22, 8/11 or 26/26, respectively. Degenerative changes in the liver and kidney were the primary effects of exposure, but the adrenal degeneration

seen in rats was not noted in mice. Repeated exposure to 400 ppm 1,2-dichloropropane (7 hours/day, 5 days/week for 1-12 days) produced mortality in mice with histologic liver and kidney damage as detailed in the Subchronic Toxicity Section and Table V-2 (Heppel et al., 1948). Sidorenko et al. (1976) exposed mice to single vapor exposures of 26.0, 22.0, 17.5, 12.6 or 4.8 mg/ℓ 1,2-dichloropropane for an unspecified length of time and observed general agitation, decreased coordination, sluggishness, amyotonia, sporadic clonic spasms and loss of righting reflex. The onset of these effects was reported to be dose-related.

Highman and Heppel (1946) also exposed guinea pigs to 2200 ppm (~10,400 mg/m³) 1,2-dichloropropane for single 4- or 7-hour exposures, or for 2, 3 or 4 consecutive daily 7-hour exposures. Histological effects observed among animals treated at this level included fatty degeneration of the liver and kidney, extensive coagulation and focal hemorrhagic necrosis of the adrenal cortex and congestion of the adrenal medulla. Guinea pigs exposed to 2200 ppm (~10,400 mg/m³) 7 hours/day for five exposures experienced lacrimation followed by conjunctival swelling, weight loss, roughening of the fur and coarse breathing. Of the 16 guinea pigs exposed on this schedule, 11 died by the fifth exposure. Guinea pigs exposed repeatedly to 6500 mg/m³ (~1500 ppm) 1,2-dichloropropane (7 hours/day, 5 days/week) exhibited drowsiness, decreased growth, 28% mortality (5/18) after 6 or 11 exposures, and subcortical fibrosis of the adrenals (Subchronic Toxicity Section and Table V-2) (Heppel et al., 1946). Repeated exposures to 1000 or 400 ppm 1,2-dichloropropane did not appear to be lethal for guinea pigs (see Table V-2) (Heppel et al., 1946, 1948); subcortical fibrosis was a marked histological effect of the 1000 ppm exposures, but minimal histological effects were elicited by exposure to 400 ppm.

TABLE V-2

Effects of Subchronic Exposure of Experimental Animals to 1,2-Dichloropropane

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/F344/N	male/10	~136 g/ 7-8 weeks	~99.4%[a]	gavage/ corn oil	0, 60, 125, 250, 500 or 1000 mg/kg bw	5 days/week for 13 weeks	All males and females at 1000 mg/kg dose level died and 5/10 males receiving 500 mg/kg died; mean terminal body weights were depressed 16% in males and 8% in females at 500 mg/kg; centrilobular congestion of the liver occurred in 5/10 males and 2/10 females at 1000 mg/kg level; hepatic fatty changes and centrilobular necrosis were observed in 2/10 females at 1000 mg/kg dose level; histopathological examinations were conducted only in the 0, 500 and 1000 mg/kg groups.	NTP, 1983 draft
	female/10	~100 g/ 7-8 weeks	~99.4%[a]	gavage/ corn oil	0, 60, 125, 250, 500 or 1000 mg/kg bw	5 days/week for 13 weeks		
Rat/NR	NR/NR	NR/NR	NR	oral/NR	14.4 or 360 mg/kg bw	30 days	Increase in blood serum cholesterol, beta-lipoproteins and gamma globulin by day 10; serum pseudocholinesterase inhibited by day 20; fructose-1-monophosphate adolase, alanine transaminase and asparagine transaminase were stimulated by day 20; analine transaminase was inhibited by day 30; results reported in an abstract.	Kurysheva and Ekshtat, 1975
Rat/NR	male/13, female/5	162 g/NR	NR[b]	inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, 5 days/week for 35 exposures	8/18 died after 1-35 exposures[c], 1/14 controls died; reversible unsteadiness; growth adversely affected, but not quantified; centilobular fatty degeneration in livers of 2/9 examined; "several" showed increased hemosiderin in spleen.	Heppel et al., 1946

TABLE V-2 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/Wistar	male/5, female/22	215 g/NR	NR[b]	inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day 5 days/week for 97 exposures	9/27 died after 6-32 exposures, 1/18 controls died; depressed weight apparent result of decreased food consumption; signs of intoxication (rough fur, crusty eyes, coarse breathing, weakness) noted before death.[d]	Heppel et al., 1946
Rat/Sprague-Dawley	male/12	210 g/NR	NR[b]	inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day 5 days/week for 47 exposures	12/12 died after 10-47 exposures, 0/13 controls died; more sensitive than Wistar strain; signs of intoxication before death (see Wistar response).[d]	Heppel et al., 1946
Rat/Sprague-Dawley	male/6	120 g/NR	NR[b]	inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day, 5 days/week for 93 exposures	4/6 died after 17-59 exposures, 0/6 controls died; more sensitive than Wistar strain; signs of intoxication before death (see Wistar response).[d]	Heppel et al., 1946
Rat/NR	male/26, female/23	260 g/NR	NR[b]	inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 140 exposures	3/49 died after 108-134 exposures, 0/30 controls died; depressed weight gain, but no signs of toxicity; histological examination of 75 rats after 3-140 exposures showed slight hemosiderin deposition in the liver.	Heppel et al., 1948
Mouse/B6C3F1	male/10	~24 g/ 15 weeks	~99.4%[a]	gavage/ corn oil	0, 30, 60, 125, 250 or 500 mg/kg bw	5 days/week for 13 weeks	One male at 60 mg/kg dose level died and one female at 500 mg/kg dose level died; mean terminal body weights were depressed 5, 1.1, 1.4 and 4.4% in the 500, 125, 60 and 30 mg/kg males, respectively, and 3.6, 3.2, 0.4 and 1.1% in the 500, 250, 60 and 30 mg/kg females, respectively; compound-related histopathologic effects were not observed, but only 0 and 500 mg/kg groups were examined.	NTP, 1983 draft
	female/10	~22 g/ 15 weeks	~99.4%[a]	gavage/ corn oil	0, 30, 60, 125, 250 or 500 mg/kg bw	5 days/week for 13 weeks		

TABLE V-2 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Mouse/C57	NR/16	NR	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 1-12 exposures	Mortality data incompletely reported; slight fatty degeneration in liver of 5/8 that died or were killed after the first exposure; slight fatty degeneration of kidney in 1/2 killed after 2 exposures; histological effects not noted in other exposed or 5 controls.	Heppel et al., 1948
Mouse/C3H	NR/80	NR/NR	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	4-7 hours/day, 5 days/week for 37 exposures	"most" of the mice died during the study; of an unspecified number that received 14-28 exposures, 9 showed liver congestion and fatty degeneration, 7 showed liver centrilobular necrosis, and 6/8 showed kidney fatty degeneration. Hepatomas also occurred.	Heppel et al., 1948
Guinea pig/ NR	male/7, female/11	588 g/NR	NR[b]	Inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, 5 days/week for 39 exposures	5/18 died after 6 or 11 exposures, 1/25 controls died; drowsiness; growth adversely effected but not quantified; subcortical fibrosis of adrenals in 9/9 examined, but no significant hepatic effects.	Heppel et al., 1946
Guinea pig/ NR	male/12	800 g/NR	NR[b]	Inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day, 5 days/week for 126 exposures	3/12 died after 22-97 exposures, 1/14 controls died. Subcortical fibrosis of adrenals in 9/9 examined after 126 exposures.	Heppel et al., 1946
Guinea pig/ NR	male/2, female/14	640 g/young	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 134 exposures	3/16 died after 63-111 exposures, 8/24 controls died; minimal hemosiderin deposition in the spleen and adrenals and minimal fatty changes in the liver, kidney and heart[c].	Heppel et al., 1948
Guinea pig/ NR	male/10, female/6	1072 g/mature	NR[b]	Inhalation/NA	400 ppm (~1850 mg/m³)	7 hours/day, 5 days/week for 134 exposures	4/16 died after 3-97 exposures, 4/18 controls died. Minimal histological effects as described for young guinea pigs above[c].	Heppel et al., 1948

TABLE V-2 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rabbit/NR	male/1, female/3	2270 g/NR	NR[b]	Inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, 5 days/week for 39 exposures	1/4 died after 26 exposures 0/4 controls died; no adverse effects on appearance or weight gain; no significant histological lesions in 3/3 examined.	Heppel et al., 1946
Rabbit/NR	male/4	3.7 kg/NR	NR[b]	Inhalation/NA	4400 mg/m³ (~1000 ppm)	7 hours/day, 5 days/week for 126 exposures	0/4 died, 0/4 controls died; no significant histological lesions; normal blood cell count and hemoglobin[f].	Heppel et al., 1946
Dog/NR	NR/1	NR/NR	NR[b]	Inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, for 6 exposures	No obvious "ill effects."	Heppel et al., 1946
Dog/NR	NR/9[g]	3.4-9.5 kg/NR	NR[b]	Inhalation/NA	6500 mg/m³ (~1500 ppm)	7 hours/day, 5 days/week for 55 exposures (2 pups) or 128 exposures (2 pups and 5 adults)	3/5 adults and 1/4 puppies died after 27-28 (adult) and 96 (puppy) exposures; 0/3 adult and 0/1 pup controls died; fatty degeneration of liver and convoluted tubules of kidney in the 4 dogs that died; fatty degeneration of heart and adrenal cortex in 2/4 that died; no significant histopathological effects in survivors; blood count and hemoglobin[f] and liver and kidney function tests[h] normal in dead and surviving dogs.	Heppel et al., 1946
Dog/NR	female/5	9.2 kg/NR	NR[b]	Inhalation/NA	400 ppm (1850 mg/m³)	7 hours/day, 5 days/week for 128 exposures	0/5 died, 0/5 control died; slight hemosiderosis in the spleen in 5/5, scattered granulomatous lesions in kidney of 2/5.	Heppel et al., 1948

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TABLE V-2 (cont.)

Species/Strain	Sex/Number	Weight/Age	Purity	Route/Vehicle	Dose/Exposure	Duration	Effect	Reference
Rat/NR	NR/20	NR/NR	NR	Inhalation/NA	9 mg/m³ (1.9 ppm)	94 days	Disruption of CNS function, blood enzyme activity, DNA synthesis by the liver and biological oxidation in the liver, lungs and adrenals; results reported in an abstract.	Tsulaya et al., 1977

[a]Reagent grade 1,2-dichloropropane that contained 0.24% toluene.

[b]A commercial product with unknown precise composition was used; it was noted that the results of "precision distillation" of this product in a 4-foot fractionating column indicated that it "probably contained a considerable percentage of other isomers."

[c]Three of the rats were sacrificed after 10 exposures.

[d]Four rats of unspecified strain that died after 7 exposures showed moderate to marked fatty degeneration of the liver, kidneys and heart and splenic hemosiderosis. 18 rats of unspecified strain that were killed after 23-97 exposures showed moderate to marked splenic hemosiderosis, but 16 controls killed at the same time showed slight to moderate splenic hemosiderosis.

[e]12 unspecified guinea pigs were killed immediately after 134 exposures and compared histologically with 17 control animals of the same age. Seven unspecified guinea pigs were killed 6-8 months after the completion of 134-137 exposures and compared with 5 controls.

[f]Red and white cell counts, differential counts and hemoglobin determination were conducted at intervals of ~1 month on all exposed dogs and rabbits exposed to 1000 ppm, and on 4 control rabbits and 3 control dogs.

[g]Five adults and four puppies

[h]Determination of prothrombin time, bromsulfalein excretion, total plasma proteins, A/G ratio, plasma N.P.N. and serum phosphatase were done on "one or two occasions" for each of the 3 adult dogs that died, but some of the determinations were made "within 6 days of death." The 2 surviving adult dogs were tested for bromsulfalein excretion, serum phosphatase level, prothrombin time, total plasma protein, albumin, nonprotein nitrogen, sugar, acetone, bile pigments and abnormal cellular constituents. Determinations of prothromin time, bromsulfalein excretion, serum phosphatase, icterus index, total protein, albumin and nonprotein nitrogen were conducted on the 4 exposed and 1 control puppy.

NA = Not applicable; NR = Not reported

Treatment-related effects were not observed in rabbits exposed by inhalation to 4400 mg/m³ (~1000 ppm) or 6900 mg/m³ (~1600 ppm) 1,2-dichloropropane for 7 hours (Heppel et al., 1946) (see Table V-1). At 2200 ppm (~10,400 mg/m³), 50% mortality (2/4) was observed after 2 exposures and degenerative changes were apparent in the liver and kidneys.

Subchronic Toxicity. Subchronic oral toxicity studies were conducted by NTP (1983 draft) to determine the doses to be used in a chronic carcinogenicity bioassay of 1,2-dichloropropane. In these range-finding studies, groups of 10 F344/N rats and 10 B6C3F$_1$ mice of each sex were gavaged with reagent grade 1,2-dichloropropane (~99.4% pure) in corn oil, 5 days/week for 13 weeks at doses of 0, 60, 125, 250, 500 or 1000 mg/kg bw (rats) and 0, 30, 60, 125, 250 or 500 mg/kg bw (mice). Body weight measurements and clinical examinations were conducted weekly; necropsies were performed on all animals. Comprehensive histopathological examinations were conducted on the control, 500 and 1000 mg/kg bw groups of rats, and on the control and 500 mg/kg bw groups of mice.

All of the male and female rats in the 1000 mg/kg bw (714.3 mg/kg bw/day) dose groups and 5 of 10 males in the 500 mg/kg bw (357 mg/kg bw/day) dose groups died (see Table V-2) (NTP, 1983 draft). Terminal mean body weights were depressed 16% in males and 8% in females that received 500 mg/kg bw (375 mg/kg bw/day). Non-neoplastic hepatic lesions were found in the high-dose (1000 mg/kg bw) rats of both sexes; these included centrilobular congestion (5/10 males, 2/10 females) and fatty changes and centrilobular necrosis (4/10 females). Treatment-related mortality, terminal body weight depression or histopathological effects were not described in the mice of either sex (see Table V-2).

The only other subchronic oral toxicity data that are available were reported in an English abstract of a Soviet study. Kurysheva and Ekshtat (1975) administered daily doses of 14.4 or 360 mg 1,2-dichloropropane/kg bw to an unspecified number of rats for 30 days, but the method and frequency of oral administration were not stated. Blood serum cholesterol, beta-lipoproteins and gamma globulin levels were reportedly increased by day 10, serum pseudocholinesterase was inhibited by day 20, fructose 1-monophosphate aldolase, alanine transaminase and asparagine transaminase were stimulated by day 20, and alanine transaminase was inhibited by day 30. Additional information regarding the design or results of this study were not provided.

Information on the subchronic inhalation toxicity of 1,2-dichloropropane is available from the studies of Heppel et al. (1946, 1948). In these studies, rats, mice, guinea pigs and rabbits were exposed for 7 hours daily, "nearly always" 5 days/week for different durations to concentrations of 10,400 mg/m³ (~2200 ppm), 6500-6900 mg/m³ (~1500-1600 ppm), 4400 mg/m³ (~1000 ppm) and ~1850 mg/m³ (400 ppm) 1,2-dichloropropane. A limited number of dogs were similarly exposed to 1500, 1000 and 400 ppm 1,2-dichloropropane and unexposed control animals were employed at each dose level for all species. The design and results of these studies are summarized in Table V-2. Signs of intoxication were described and autopsies were reportedly conducted on all of the exposed and "many" of the control animals, but it should be noted that the results of gross and histological tissue examinations were ambiguous and reported incompletely, that the extent of histological examination was unclear, and that particularly small numbers of rabbits and dogs were exposed at each dose level. Blood cell counts and hemoglobin determinations were conducted on all rabbits and dogs exposed to

1000 ppm 1,2-dichloropropane, and liver and kidney function tests were conducted on selected dogs exposed to 1000 ppm. The 1,2-dichloropropane used in these experiments, however, was a commercial product that "probably contained a considerable percentage of other isomers."

As detailed in the Acute Toxicity Section, exposure of rats, mice, guinea pigs and rabbits to 2200 ppm 1,2-dichloropropane (7 hours/day, 5 days/week) produced signs of acute toxicity in all these species with mortality after 5 or 8 exposures (rats, guinea pigs) or 2 exposures (rabbits) (Heppel et al., 1946); mice were the most sensitive with 10/11 dying during the first exposure. Rats, guinea pigs and rabbits that were exposed to ~1600 ppm 1,2-dichloropropane for 5 consecutive days survived the exposures (except for 1 of 2 rabbits) and appeared only to exhibit minimal signs of toxicity (see Acute Toxicity Section), but mice were not tested at this dose level. Exposure to ~1500 ppm for 35-39 exposures produced signs of CNS depression (e.g., unsteadiness, drowsiness), mortality starting in the first and second weeks of exposure and growth depression in rats and guinea pigs. Rabbits were generally unaffected and all mice died after a single 2- to 4-hour exposure. Similar results were obtained at ~1000 ppm with these species and with dogs, except that the responses were less marked and deaths occurred somewhat later in the experiment. The mice, as with the higher concentrations, were killed by a single 2-4 hour exposure to ~1000 ppm 1,2-dichloropropane. Animals that died from the exposures to ~1000-2000 ppm 1,2-dichloropropane had histological evidence of liver (fatty degeneration, coagulation necrosis) and kidney (fatty degeneration) damage, and the adrenal cortex in guinea pigs showed fibrosis. With the exception of splenic hemosiderosis (rats) and adrenal subcortical fibrosis (guinea pigs), survivors did not appear to exhibit significant histological effects of

exposure. The hematological, liver function and kidney function analyses of the dogs and rabbits did not indicate significant treatment-related effects.

In the second study, rats, guinea pigs and dogs received 128-140 seven-hour exposures (5 days/week) of 400 ppm 1,2-dichloropropane (see Table V-2) (Heppel et al., 1948). The only significant adverse effect in these three species which was attributable to exposure was a decreased weight gain in the rats (-10% in males, -15% in females). In the same study, mice were similarly exposed to 400 ppm 1,2-dichloropropane 7 hours/day, 5 days/week. Mortality data were incompletely reported, but C57 and C3H mice died as a result of exposure to 400 ppm 1,2-dichloropropane; the C57 mice started dying after the first exposure. C57 mice that died or were killed after one to two 7-hour 400 ppm exposures showed slight fatty degeneration of the liver and kidneys. These effects appeared to be more severe in C3H mice receiving the 14-28 4- to 7-hour exposures resulting in moderate to severe congestion, fatty degeneration of the liver and extensive centrilobular coagulation necrosis of the liver, and slight to moderate fatty degeneration of the kidney. "Most" of the 80 C3H mice exposed to 400 ppm 1,2-dichloropropane died during the 37-exposure study, and only 3/80 C3H mice survived the exposures followed by a 7-month observation period; the 3 survivors had multiple hepatomas, but other histological effects were not noted.

It was reported in an abstract of a Soviet study that exposure to 9 mg/m^3 1,2-dichloropropane (~1.9 ppm) for 20 days elicited disruption of CNS function, blood enzyme activity, DNA synthesis (liver), and biological oxidation (liver, lungs and adrenals) in a group of 20 rats (Tsulaya et al., 1977). Additional details regarding the design and results of this study were not reported.

Chronic Toxicity. The only data regarding the non-neoplastit effects of chronic exposure to 1,2-dichloropropane are available from a National Toxicology Program carcinogenesis bioassay (NTP, 1983 draft). As detailed in the Carcinogenicity Section, groups of 50 female F344/N rats and 50 B6C3F$_1$ mice of each sex were gavaged with reagent grade 1,2-dichloropropane (~99.4% pure) in corn oil at doses of 0 (vehicle control), 125 or 250 mg/kg bw, 5 days/week for 103 weeks; groups of 50 male F344/N rats were similarly exposed to doses of 0, 62 or 125 mg/kg bw.

A dose-related depression in mean body weight was observed in dosed rats of both sexes throughout most of the study (NTP, 1983 draft). The final body weights for the low-dose males, low-dose females, high-dose males and high-dose females were 5%, 5%, 14% and 24% less than control values, respectively. Survival was significantly ($p<0.001$) reduced in the high-dose female rats, but not in the low-dose female or male rats. In male rats 39/50 (78%) of the control, 42/50 (84%) of the low-dose, and 41/50 (82%) of the high-dose groups lived to the end of the study (105-108 weeks). In female rats 37/50 (74%) of the vehicle control, 43/50 (86%) of the low-dose, and 16/50 (32%) of the high-dose groups lived to the end of the study. The high-dose females had increased incidences of non-neoplastic liver lesions, although there was no increase in the incidence of liver tumors in the female rats (see Carcinogenicity Section); foci of clear cell change were found in 3/50 (6%) of the control, 5/50 (10%) of the low-dose and 11/50 (22%) of the high-dose groups. Necrosis (focal and centrilobular combined) occurred in 2/50 (4%) of the control, 1/50 (2%) of the low-dose and 12/50 (24%) of the high-dose groups of female rats. Mammary gland hyperplasia was increased in the low-dose but not high-dose female rats (controls, 10/50;

low-dose, 20/50; high-dose, 1/50). This finding might possibly be due to the poor survival and an increased incidence of adenocarcinoma in the high-dose females (see Carcinogenicity Section). Treatment-related non-neoplastic effects were not observed in male rats.

Mean body weights of the treated and control mice were comparable throughout the course of the bioassay (NTP, 1983 draft). Survival was reduced in the female mice [controls, 35/50 (70%); low-dose, 29/50 (58%); high-dose, 26/50 (52%)] after 105-107 weeks of exposure. The reduction in survival was statistically significant in the high-dose group. Infections of the reproductive tract, however, may have contributed to the decreased survival of the female mice; suppurative inflammation was found in the ovary, uterus or multiple organs of 5/11 control, 9/14 low-dose and 14/22 high-dose females that died before the end of the study. 1,2-Dichloropropane caused nonneoplastic liver lesions in male mice that included hepatomegaly (control, 3/50; low-dose, 5/49; high-dose, 15/50) and focal and centrilobular necrosis (control, 2/50; low-dose, 5/49; high-dose, 10/50). These lesions did not occur at increased incidences in treated female mice, but liver tumors were increased in both males and females (see Carcinogenicity Section). Acanthosis of the forestomach surface epithelium occurred at increased incidences in the high-dose males (control, 0/50; low-dose, 0/48; high-dose, 2/49) and low- and high-dose females (control, 0/50; low-dose, 5/50; high-dose, 4/50), a finding consistent with a slightly increased occurrence of forestomach squamous cell papillomas (see Carcinogenicity Section).

Target Organ Toxicity

The principal target organ for non-neoplastic effects of orally administered 1,2-dichloropropane in rats and mice is the liver (NTP, 1983 draft). As detailed in the Subchronic Toxicity Section, hepatic lesions were found in male (centrilobular congestion) and female (centrilobular congestion, fatty changes and necrosis) F344/N rats that were gavaged with 1000 mg 1,2-dichloropropane/kg bw in corn oil, 5 days/week for 13 weeks. In the 2-year carcinogenesis bioassay (Carcinogenicity Section), treatment-related hepatic effects were found in female F344/N rats (foci of clear cell change, focal and centrilobular necrosis) and male $B6C3F_1$ mice (hepatomegaly, focal and centrilobular necrosis) that were exposed 5 days/week to 250 mg/kg bw. Similar hepatic effects were described in dogs 4 days following the administration of single oral doses of ~230-580 mg 1,2-dichloropropane/kg bw (Wright and Schaffer, 1932).

The liver also appears to be affected during acute and subchronic inhalation exposure to 1,2-dichloropropane (Highman and Heppel, 1946; Heppel et al., 1946, 1948; Sidorenko et al., 1976; Belyaeva et al., 1977). As detailed in the Acute Toxicity and Subchronic Toxicity Sections, laboratory rodents that died from several (<12) repeated daily 7-hour exposures of 1,2-dichloropropane at 1000-2200 ppm and mice that died or were killed after 14-28 4- to 7-hour exposures of 400 ppm exhibited liver histologic effects such as congestion, fatty degeneration and necrosis (Highman and Heppel, 1946; Heppel et al., 1946, 1948). Hepatic centrilobular necrosis was noted in rats treated for 2 days at 2200 ppm for 7 hours daily and became progressively more severe when treatment was extended (see Table V-2). Sidorenko et al. (1976) reported hepatic perilobular hyperplasia and hypertrophy,

reduction of centrilobular ribonuclear proteins, and reduced hepatic enzyme activity in rats treated at 216 or 432 ppm continuously for 7 days. Slight fatty degeneration of the liver was reported in C57 mice treated with 400 ppm 1,2-dichloropropane for 7 hours (Heppel et al., 1948). Similar liver histopathologic effects were noted in guinea pigs treated at 2200 ppm with a single 4- or 7-hour exposure or with 2, 3 or 4 daily 7-hour exposures. Corroboratively, Drew et al. (1978) reported significantly increased activities of SGOT, SGPT, and serum OCT in rats that were exposed to 1000 ppm 1,2-dichloropropane for a single 4-hour exposure.

Although the liver appears to be the primary target for 1,2-dichloropropane, the kidneys and adrenal gland are also important target organs. Gross observation of the kidneys of rats and mice exposed to 1,2-dichloropropane by gavage at doses of 2000 mg/kg bw/day and 500-1000 mg/kg/day, respectively, for 14 consecutive days showed the presence of red medullae (NTP, 1983 draft). Histopathological effects in the kidney and adrenal medulla have also been described in rats and guinea pigs following inhalation exposure to 2200 ppm 1,2-dichloropropane for 4 or 7 hours (Highman and Heppel, 1946; Heppel et al., 1946); subchronic exposure to lower levels (1000 and 1500 ppm) also elicited adrenal effects (subcortical fibrosis) in guinea pigs (Heppel et al., 1946). Fatty degeneration of the kidney was observed in mice exposed by inhalation to 400 ppm 1,2-dichloropropane 4-7 hours/day, 5 days/week for 14-28 exposures (Heppel et al., 1948). Histological damage and suppression of oxidative enzymes were reported in the kidneys of rats treated with 216 or 432 ppm 1,2-dichloropropane continuously for 7 days (Sidorenko et al., 1976).

Other Effects

Carcinogenicity. In a draft of a carcinogenesis bioassay of 1,2-dichloropropane groups of 50 female F344/N rats, 50 male B6C3F$_1$ mice and 50 female B6C3F$_1$ mice were administered 1,2-dichloropropane in corn oil by gavage at doses of 0 (vehicle control), 125 or 250 mg/kg bw, 5 days/week for 103 weeks (calculated to 7 days/week these doses are 0, 89.3 or 178.6 mg/kg bw/day, respectively) (NTP, 1983 draft). [Note: A final NTP report is in preparation.] Groups of 50 male F344/N rats received doses of 0, 62 or 125 mg/kg bw on the same schedule (0, 44.3 or 89.3 mg/kg bw/day, respectively). The 1,2-dichloropropane was reagent grade with an approximate purity of 99.4% (toluene was identified as an impurity constituting 0.24% v/v of the product). The animals were 6-9 weeks of age at the start of the treatment. Necropsies with comprehensive histological examinations were performed on all animals found dead and on those killed at the end of the study, unless precluded by autolysis or cannibalization. As detailed in the Chronic Toxicity Section, survival was significantly reduced in the high-dose (250 mg/kg bw) female rats and female mice. Because of the reduced survival, statistical procedures adjusted for intercurrent mortality (life table and incidental tumor tests) were regarded as more meaningful than unadjusted analysis (Fischer exact test, Cochran-Armitage test for linear trend) (NTP, 1983 draft). The design and results of the NTP (1983 draft) bioassay of 1,2-dichloropropane are summarized in Table V-3.

Neoplastic lesions were not significantly increased in the treated male rats (NTP, 1983 draft). Islet-cell carcinomas of the pancreas occurred with a positive trend (significant Cochran-Armitage test) in male rats (see Table V-3), but this response was not considered to be treatment-related because

TABLE V-3

Summary of Gavage Carcinogenesis Bioassay of 1,2-Dichloropropane[a]

Species/ Strain	Sex[b]	Dose[c] (mg/kg bw)	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P value)[d]
Rat/ F344/N	M	125	5 days/week for 103 weeks	105-108 weeks	Pancreas (Islet cell)	adenoma	3/50 (6%)
						carcinoma	3/50 (6%)
						adenoma or carcinoma	6/50 (12%)
		62	5 days/week for 103 weeks	105-108 weeks	Pancreas (Islet cell)	adenoma	1/50 (2%)
						carcinoma	0/50 (0%)
						adenoma or carcinoma	1/50 (2%)
		0 (vehicle control)	5 days/week for 103 weeks	105-108 weeks	Pancreas (Islet cell)	adenoma	4/48 (8%)
						carcinoma	0/48 (0%) (p=0.04)
						adenoma or carcinoma	4/48 (8%)
Rat/ F334/N	F	250	5 days/week for 103 weeks	105-108 weeks	Mammary gland	adenocarcinoma	5/50 (10%)[e]
						fibroadenoma	7/50 (14%) (p=0.05N)[f]
					Uterus	endometrial stromal polyp	11/50 (22%)
					Pituitary	adenoma	10/46 (22%)
						carcinoma	0/46 (0%)
						adenoma or carcinoma	10/46 (22%)

TABLE V-3 (cont.)

Species/ Strain	Sex[b]	Dose[c] (mg/kg bw)	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P value)[d]
Rat/ F344/N	F	125	5 days/week for 103 weeks	105-108 weeks	Mammary gland	adenocarcinoma	2/50 (4%)
						fibroadenoma	20/50 (40%)
					Uterus	endometrial stromal polyp	17/49 (35%)
					Pituitary	adenoma	26/50 (52%) (p=0.04)[f]
						carcinoma	2/50 (4%)
						adenoma or carcinoma	28/50 (56%)
		0 (vehicle control)	5 days/week for 103 weeks	105-108 weeks	Mammary Gland	adenocarcinoma	1/50 (2%)[e]
						fibroadenoma	15/50 (30%) (p=0.05N)[f]
					Uterus	endometrial stromal polyp	10/50 (20%)[g]
					Pituitary	adenoma	16/49 (33%)
						carcinoma	3/49 (6%)
						adenoma or carcinoma	19/49 (39%)
Mouse/ B6C3F$_1$	M	250	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	16/50 (32%) (p=0.03)
						carcinoma	16/50 (32%)
						adenoma or carcinoma	32/50 (64%) (p=0.02)
		125	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	10/49 (20%)
						carcinoma	16/49 (33%)
						adenoma or carcinoma	25/49 (51%)

TABLE V-3 (cont.)

Species/ Strain	Sex[b]	Dose[c] (mg/kg bw)	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P value)[d]
Mouse/ B6C3F$_1$	M	0	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	7/50 (14%) (p=0.02)
						carcinoma	11/50 (22%)
						adenoma or carcinoma	18/50 (36%) (p=0.003)
Mouse/ B6C3F$_1$	F	250	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	5/50 (10%) (p=0.03)
						carcinoma	4/50 (8%)
						adenoma or carcinoma	9/50 (18%) (p=0.004)
					Thyroid follicular cell	adenoma	3/46 (7%)
						carcinoma	2/46 (4%)
						adenoma or carcinoma	5/46 (11%)[e]
Mouse/ B6C3F$_1$	F	125	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	4/50 (8%)
						carcinoma	3/50 (6%)
						adenoma or carcinoma	7/50 (14%) (p=0.03)
					Thyroid follicular cell	adenoma	0/45 (0%)
						carcinoma	0/45 (0%)
						adenoma or carcinoma	0/45 (0%)

TABLE V-3 (cont.)

Species/ Strain	Sex[b]	Dose[c] (mg/kg bw)	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P value)[d]
Mouse/ B6C3F$_1$	F	0 (vehicle control)	5 days/week for 103 weeks	105-107 weeks	Liver	adenoma	0/50 (0%) (p=0.03)
						carcinoma	1/50 (2%)
						adenoma or carcinoma	1/50 (2%) (p=0.01)
					Thyroid follicular cell	adenoma	1/48 (2%)
						carcinoma	0/48 (0%)
						adenoma or carcinoma	1/48 (2%) (p=0.03)

[a]Source: NTP, 1983 draft

[b]50 animals/sex/dose tested

[c]Reagent grade 1,2-dichloropropane (~99.4% pure, containing 0.24% toluene) was administered in corn oil vehicle.

[d]The probability levels for the Fischer exact test and Cochran-Armitage test for linear trend are given beneath the incidence of tumors in the dosed and control groups, respectively, when p<0.05. All values are nonsignificant unless other wise indicated.

[e]Significant (p<0.05) when adjusted for intercurrent mortality (life table and incidental tumor tests).

[f]Not significant (p>0.05) when adjusted for intercurrent mortality (life table and incidental tumor tests).

[g]Significant (p<0.05) when adjusted for intercurrent mortality (life table test).

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the Fischer exact, life table and incidental tumor tests were not significant. In female rats, a significant dose-related increase in mammary gland adenocarcinomas (control, 1/50; low-dose, 2/50; high-dose, 5/50) was found after adjustment for intercurrent mortality. The majority of these tumors were found at the end of the study (control, 1/37; low-dose, 2/43; high-dose, 4/16), and it was noted that mammary gland adenocarcinomas are relatively uncommon in female F344/N rats (incidences in historical controls for the testing laboratory and for all NTP testing laboratories combined were 3/150 and 11/895, respectively). Mammary fibroadenomas were decreased in the high-dose female rats (control, 15/50; low-dose, 20/50; high-dose, 7/50). Endometrial stromal polyps occurred with a statistically significant positive trend (life table test), but the incidence was not significantly increased in the low- or high-dose groups. An increased incidence of pituitary adenomas in the low-dose females was statistically significant as determined by the Fischer exact test, but this increase was not significant when survival differences were taken into account (life table and incidental tumor tests) and the incidence of pituitary carcinomas was greater in the control than in the treated female rats. The high dose (250 mg/kg bw), however, was toxic for the female rats as reflected by reduced survival late in the study and lowered body weights (see Chronic Toxicity Section). The high-dose female rats also had increased incidences of non-neoplastic liver changes (see Chronic Toxicity Section), but there was no increase in the incidence of liver tumors.

Statistically significant dose-related increases of liver adenomas occurred in both male (control, 7/50; low-dose, 10/49; high-dose, 16/50) and female (control, 0/50; low-dose, 4/50; high-dose, 5/50) mice (see Table V-3)

(NTP, 1983 draft). The treated mice also had slightly higher incidences of liver carcinomas (male: control, 11/50; low-dose, 16/49; high-dose, 16/50; female: control, 1/50; low-dose, 3/50; high-dose, 4/50), but the increases were not statistically significant. As detailed in the Chronic Toxicity Section, non-neoplastic liver lesions were increased in male but not in female mice. The combined incidence of thyroid follicular cell adenomas or carcinomas was significantly elevated in the high-dose female mice after adjustment for intercurrent mortality and occurred with a significant positive trend, but no adenomas or carcinomas were observed in the low-dose female mice. 1,2-Dichloropropane was not, however, concluded to be a thyroid tumorigen in the female mice, apparently because the uncombined incidences of follicular cell adenomas and carcinomas were not significantly elevated. Squamous cell papillomas of the forestomach also occurred in the dosed male and female mice [males: control, 0/50 (0%); low-dose, 1/48 (2%); high-dose, 3/49 (6%), females: control, 0/50 (0%); low-dose, 2/50 (4%); high-dose, 2/50 (4%)]. The results of statistical analyses of these data were not reported, but it was noted that the historical incidences of squamous cell papillomas of the forestomach for the testing laboratory and for all NTP testing laboratories combined were 0/146 and 2/855 (0.2%), respectively, for males and 0/147 and 3/879 (0.3%), respectively, for females.

NTP (1983 draft) concluded that the increased incidences of hepatocellular adenomas provided "some" evidence that 1,2-dichloropropane was carcinogenic for both male and female $B6C3F_1$ mice and that this evidence was strengthened by the slightly increased incidences of hepatocellular carcinomas in both sexes of mice. The increased incidence of mammary gland adenocarcinomas provided equivocal evidence of carcinogenicity in female F344/N

rats because the increase was marginal and occurred only at the high dose level, which was toxic. No evidence of carcinogenicity for male F344/N rats was found.

In the only other study that reported neoplastic effects, 80 C3H mice were exposed by inhalation for 4-7 hours/day, 5 days/week to 400 ppm (1849 mg/m³) 1,2-dichloropropane (Heppel et al., 1948). After 37 exposures, the surviving mice ("most" died during the exposure period) were held for an observation period of 7 months. Only three mice survived to the end of the observation period with each exhibiting multiple hepatomas. The significance of these data is uncertain because of the high mortality. Additional detail regarding the design of this study is presented in the Subchronic Toxicity Section.

Mutagenicity. Mutagenicity and clastogenicity assays of 1,2-dichloropropane are summarized in Table V-4. In the reverse mutation assay with Salmonella typhimurium, 1,2-dichloropropane was mutagenic only in strains TA1535 and TA100. Both strains are sensitive to the production of mutations by base-pair substitutions. Negative results were obtained by NTP (1983 draft) in plate incorporation assays at concentrations up to 2 mg/plate; however, De Lorenzo et al. (1977), Stolzenberg and Hine (1980), and Carere and Morpurgo (1981) reported positive results with concentrations of 10-50 mg/plate, both with and without activation by hepatic S9 mix. Positive results have also been obtained in spot tests (Carere and Morpurgo, 1981; Principe et al., 1981). Thus, at high concentrations, 1,2-dichloropropane appears to induce base-pair substitutions in S. typhimurium.

TABLE V-4

Mutagenicity/Clastogenicity of 1,2-Dichloropropane

Assay	Indicator/	Application	Concentration or Dose	Response +S9	Response -S9	Comment	Reference
Reverse mutation (histidine independence)	S. typhimurium TA100 TA1535	plate incorporation	10, 20 or 50 mg/plate	+ +	+ +	NC	DeLorenzo et al., 1977
Reverse mutation (histidine independence)	S. typhimurium TA100	plate incorporation	100 µmoles/plate	+	+	(+) at 100 µmoles/plate ±S9; (-) at 1 and 10 µmoles/plate ±S9	Stolzenberg and Hine, 1980
Reverse mutation (histidine independence)	S. typhimurium TA1535 TA100	plate incorporation	1, 2.5, 5 or 10 µl/plate	+ +	+ +	NC	Carere and Morpurgo, 1981
Reverse mutation (histidine independence)	S. typhimurium TA100 TA98 TA1537 TA1535	plate incorporation	0, 33, 100, 333, 1000 or 2000 µg/plate	- - - -	- - - -	"No clearly positive response was obtained." S9's from both rat and hamster livers were used	NTP, 1983 draft
Reverse mutation (histidine independence)	S. typhimurium TA1535 TA100	spot test	0 or 10 µl/plate	+ +	+ +	NC	Principe et al., 1981
Reverse mutation (histidine independence)	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	spot test	0 or 10 µl/plate	+ - - - +	+ - - - +	1,2-Dichloropropane exerted a weak effect on the strains sensitive to mutation by base-pair substitution	Carere and Morpurgo, 1981
Foward mutation (streptomycin resistance)	Streptomyces coelicolor	plate incorporation	0, 2, 10, 20 or 100 µl/plate	NA	-	(-) at all concentrations tested	Principe et al., 1981
Forward mutation (streptomycin resistance)	Streptomyces coelicolor	plate incorporation	100-400 µl/plate	NA	-	NC	Carere and Morpurgo, 1981

TABLE V-4 (cont.)

Assay	Indicator/	Application	Concentration or Dose	Response +S9	Response -S9	Comment	Reference
Forward mutation (streptomycin resistance)	Streptomyces coelicolor	spot test	0 or 100 µL/plate	NA	-	NC	Principe et al., 1981
Forward mutation (8-azaguanine resistance)	Aspergillus nidulans	plate incorporation	0, 100, 200, 300 or 400 µL/plate	NA	+	NC	Principe et al., 1981
Foward mutation (8-azaguanine resistance, methionine suppression)	Aspergillus nidulans Strain 35 (pabaA1, anA1, yA2, meth61, nicA2, nicB8)	plate incorporation	2-100 µL/plate	NA	+	NC	Carere and Morpurgo, 1981
Forward mutation (8-azaguanine resistance)	Aspergillus nidulans	spot test	0 or 300 µL/plate	NA	+	NC	Principe et al., 1981
Sister chromatid exchange	Chinese hamster ovary cells	liquid holding	112.7, 376.0 or 1127.0 µg/mL	+	+	NC	NTP, 1983 draft
Chromosome aberration	Chinese hamster ovary cells	liquid holding	1180, 1370 or 1580 µg/mL (-S9); 460, 660 or 950 µg/mL (+S9)	+	+	NC	NTP, 1983 draft

NA = Not applicable; NC = No comment

1,2-Dichloropropane was also shown to cause forward mutation to 8-azaguanine resistance and methionine supression in Aspergillus nidulans when tested with S9 activation (Carere and Morpurgo, 1981; Principe et al., 1981), but did not cause forward mutation to streptomycin resistance in Streptomyces coelicolor when tested without S9 activation (Carere and Morpurgo, 1981; Principe et al., 1981).

1,2-Dichloropropane induced sister chromatid exchanges and chromosome aberrations in Chinese hamster ovary cells that were exposed in vitro with and without S9 metabolic activation (NTP, 1983 draft).

Teratogenicity and Other Reproductive Effects. Pertinent data regarding the teratogenic or reproductive effects of 1,2-dichloropropane were not located in the available literature.

Summary

Acute oral LD_{50}s of ~860, 2200, 2000 and 5000 mg 1,2-dichloropropane/kg bw have been reported for mice (Merck Index, 1976), rats (Smyth et al., 1969), guinea pigs (Farm Chemicals Handbook, 1980) and dogs (Wright and Schaffer, 1932), respectively. Daily administration of 1,2-dichloropropane to rats by gavage for 14 days produced 100% mortality and red renal medullae at a dose of 2000 mg/kg bw/day, and reduced body weight at 500-1000 mg/kg bw/day (NTP, 1983 draft). Similar gavage administration to mice produced mortality and red renal medullae at doses as low as 500-1000 mg/kg bw/day (NTP, 1983 draft). Treatment-related pathologic effects other than red renal medullae were not described in the rats or mice, but histological examinations were not conducted. In dogs, single oral doses of 1,2-dichlo-

ropropane in the range of 230-580 mg/kg bw elicited signs of CNS depression and histological effects that occurred primarily in the liver (e.g., congestion, slight fatty degeneration), but also in the kidney and GI tract (Wright and Schaffer, 1932).

Inhalation exposure to ~2200 ppm 1,2-dichloropropane for 7 hours/day for 5-12 days (5 days/week) produced high mortality in rats, mice, guinea pigs and rabbits (Highman and Heppel, 1946; Heppel et al., 1948). With the exception of the mice, most animals of these species tolerated exposure to lower concentrations of 1,2-dichloropropane (1600-1000 ppm). Treatment-related histological effects typically included marked visceral congestion and fatty degeneration of the liver and kidney, and fibrotic changes were frequently described in the adrenals of guinea pigs. These effects were most frequent and extensive in the animals that died and in the animals exposed to the higher levels of 1,2-dichloropropane. Drew et al. (1978) found increased activities of serum enzymes that were indicative of liver damage in rats that were exposed for 4 hours to 1000 ppm 1,2-dichloropropane. In general, except for marked splenic hemosiderosis in rats and subcortical fibrosis of the adrenal in guinea pigs, animals that survived ~35 or more exposures (5 days/week) showed only occasional minimal histopathologic effects (Heppel et al., 1946). Significant treatment-related effects were not reported in rats and guinea pigs that received from 134-140 seven-hour inhalation exposures of 400 ppm 1,2-dichloropropane (5 days/week), but there was high mortality and fatty degeneration of the liver and kidneys in mice that received 14-28 similar 400 ppm exposures (Heppel et al., 1948).

Administration of 1,2-dichloropropane by gavage to rats at doses of 1000 and 500 mg/kg bw/day 5 days/week for 13 weeks produced 100% mortality (males and females) and 50% mortality (male rats), respectively, with histopathological effects in the liver (e.g., centrilobular congestion, necrosis and fatty changes). Mice that were administered 1,2-dichloropropane at levels of 250 or 500 mg/kg/day on the same dosing schedule exhibited no treatment-related weight depression, mortality or pathologic effects.

In a carcinogenesis bioassay of 1,2-dichloropropane, rats and mice were administered doses of 0, 62 or 125 mg/kg bw (male rats) or 0, 125 or 250 mg/kg bw (female rats, mice of both sexes) for 5 days/week for 103 weeks. Dose-related weight depression was observed in the rats of both sexes, and survival was significantly reduced in the high-dose females. Significant increases in non-neoplastic liver lesions (foci of clear cell change, centrilobular necrosis) and mammary gland adenocarcinomas were found in the female rats after 105-108 weeks, but treatment-related non-neoplastic or neoplastic effects were not observed in the male rats. Survival was significantly reduced in the high-dose female mice, an effect that was possibly due to reproductive tract infection. Mean body weights were not depressed in mice of either sex. Non-neoplastic liver lesions were observed only in male mice (hepatomegaly, centrilobular necrosis), but hepatocellular adenomas were increased in both male and female mice.

1,2-Dichloropropane has been reported to induce reverse mutation (histidine independence) in S. typhimurium when tested with and without metabolic activation (De Lorenzo et al., 1977; Stolzenberg and Hine, 1980; Carere and Morpurgo, 1981; Principe et al., 1981; NTP, 1983 draft) and forward mutation

(8-azaguanine resistance, methionine supression) in A. nidulans when tested with S9 activation (Carere and Morpurgo, 1981; Principe et al., 1981), but did not cause forward mutation (streptomycin resistance) in S. coelicolor when tested without activation (Carere and Morpurgo, 1981; Principe et al., 1981). Sister chromatid exchanges or chromosome aberrations were induced in Chinese hamster ovary cells that were exposed to 1,2-dichloropropane in vitro with and without metabolic activation (NTP, 1983 draft).

Data regarding possible teratogenic or reproductive effects of 1,2-dichloropropane were not located in the available literature.

VI. HEALTH EFFECTS IN HUMANS

Pertinent data regarding the health effects of 1,2-dichloropropane in humans could not be located in the available literature; however, one abstract describing the effects of acute exposure of a 46-year-old man to an unspecified amount of 1,2-dichloropropane is reprinted below:

> Accidental ingestion of about 50 mℓ of a cleansing substance (containing 1,2-dichloropropane) in a 46-year-old man induced, within 2 hours, the appearance of a deep coma with hydriasis and hypertonia. Recovery of consciousness was obtained after 24 hours under artificial hyperventilation and osmotic diuresis. Then the patient suddenly developed an acute delirium with tremor and died at the 36th hour in a picture of irreversible shock with cardiac failure, lactic acidosis and hepatic cytolysis.
>
> Necrospy evidenced centro- and mediolobular acute hepatic necrosis. An analysis of the toxic substance by gas chromatography permited the identification of dichloropropane (Larcan et al., 1977).

Summary

One case study was located which described the effects of acute 1,2-dichloropropane exposure in a 46 year old male. Larcan et al. (1977) reported that centro- and mediolobular hepatic necrosis was revealed at autopsy in a male who accidentally ingested an unspecified amount of 1,2-dichloropropane.

VII. MECHANISMS OF TOXICITY

Specific data regarding the mechanism of 1,2-dichloropropane toxicity could not be located in the available literature. Studies of the metabolism of 1,2-dichloropropane suggest that the major metabolic pathway involves the production of a reactive intermediate, the epoxide 1,2-epoxypropane (Jones and Gibson, 1980). 1,2-Epoxypropane is an alkylating agent, whereas 1,2-dichloropropane is not (Jones and Gibson, 1980). Some of the toxic effects of 1,2-dichloropropane may be due to this reaction intermediate, rather than to the parent compound. As reviewed by the NTP (1983 draft), the centrilobular location of hepatic lesions resulting from 1,2-dichloropropane coincides with location of relatively high levels of microsomal enzymes, which activate short-chain, halogenated hydrocarbons to toxic intermediates.

1,2-Dichloropropane is known to have a number of biochemical and physiological effects as discussed previously (Chapter V, General Toxicity). Sidorenko et al. (1976) reported that the inhalation exposure of white rats to 1 or 2 mg/ℓ 1,2-dichloropropane caused suppression of enzyme activity and reduction in nucleoproteins in centrilobular sections of liver along with the suppression of oxidative enzymes and phosphomonoesterases in the kidney. Tsulaya et al. (1977) exposed rats to 9 mg/m³ 1,2-dichloropropane for 94 days and observed disruption of DNA synthesis in the liver and biological oxidation in the liver, lungs and adrenals.

Summary

Although the specific mechanism of 1,2-dichloropropane toxicity is not known, there is some evidence that the compound is metabolically activated to a toxic intermediate. 1,2-Dichloropropane has been reported to alter some biochemical parameters in the liver, kidneys, lungs and adrenals, but the toxicologic significance of these alterations is unclear.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where:

NOAEL = no-observed-adverse-effect level
LOAEL = lowest-observed-adverse-effect level
Body weight = 70 kg for adult or 10 kg for child
Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children
Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1-2 weeks). The HA values will not be used in

establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identify a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines (NRC,

1977) for selection of an uncertainty factor, but must be considered, include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen, mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water/day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and

random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Existing Guidelines and Standards

The ACGIH (1983) has adopted a TLV of 75 ppm (~350 mg/m³) and STEL of 110 ppm (~500 mg/m³) for 1,2-dichloropropane in workroom air. The TLV represents a TWA concentration for an 8-hour day or 40-hour workweek. The TLV and STEL are based primarily on the data of Heppel et al. (1946, 1948). The OSHA standard for 1,2-DCP in workplace air is also 75 ppm as an 8-hour TWA (29 CFR 1910).

The U.S. EPA (1980a) concluded that data regarding the toxicity of 1,2-dichloropropane were insufficient for the derivation of an ambient water quality criterion for the protection of human health.

Noncarcinogenic Effects

Data for the toxicity of this compound to humans are limited to a single case of acute poisoning, reported only as an abstract (Larcan et al., 1977). Centro- and mediolobular hepatic necrosis were observed in a man who died 36 hours after ingesting ~50 mℓ of a cleansing substance. The toxic material was found to contain dichloropropane, but it is unclear whether it contained other compounds as well.

Single dose oral LD_{50}s of 2200 mg/kg bw for male rats (Smyth et al., 1969), 860 mg/kg bw for mice of unspecified sex (Merck Index, 1976), and 2000 mg/kg for guinea pigs of unspecified sex (Farm Chemicals Handbook, 1980) have been reported. Nonlethal effects of single oral doses have not been described in these species in the available literature, however, the single-dose LD_{50}s for the rats and mice are consistent with lethal dose levels reported in the NTP (1983 draft) report in a 14-day gavage study.

In this 14-day study, groups of 5 male and 5 female F344 rats and 5 male and 5 female B6C3F_1 mice were gavaged with 125, 250, 500, 1000 or 2000 mg/kg bw/day of 1,2-dichloropropane in corn oil (NTP, 1983 draft). Observations included mortality, final body weights, and gross but not histologic observation of organs and tissues at necropsy. The only treatment-related effects of 1,2-dichloropropane in rats were 100% mortality and redness of the renal medullae (4/5 males, 5/5 females) at the 2000 mg/kg dose level, and reduced body weight in males and females receiving 1000 mg/kg and in males at 500 mg/kg. No effects were detected in rats administered 125 or 250 mg/kg. In mice, treatment-related effects were 100% mortality and red renal medullae in all 5 males and 5 females at 2000 mg/kg, and mortality

(5/5 males and 4/5 females) and red renal medullae (0/5 males and 3/5 females) at 1000 mg/kg. No mortality occurred at lower dosages, but red renal medullae were seen in 3/5 males and 1/5 females at 500 mg/kg and in 0/5 males and 1/5 females at each of the remaining lower dosage levels. Body weights were not adversely affected.

A single dose oral LD_{50} of 5000 mg/kg bw has been reported for dogs (Union Carbide Co., 1966). Wright and Schaffer (1932) noted that a single oral dose of 5.0 mℓ/kg bw (~5.8 g/kg bw) but not 3.0 mℓ/kg bw (~3.5 g/kg bw) was fatal to individual dogs. In lower dose experiments, 11 dogs (strain and sex not specified) were given nonlethal single doses of 0.2 to 0.5 mℓ 1,2-dichloropropane/kg bw (~230-580 mg/kg bw) by stomach tube (Wright and Schaffer, 1932). Gross pathologic examinations of all of the dogs and histologic examinations of the liver and kidney from 5 of the 11 dogs were conducted 3-4 days following administration. Gross and microscopic changes in the liver (e.g., congestion, hemorrhage, slight cloudy swelling and fatty degeneration) were evident in all 11 dogs. Symptoms of CNS depression (e.g., incoordination, loss of balance, unsteady gait, glazed eyes) were described in 5 of the 11 dogs. Renal effects (e.g., congestion, gross discoloration) and GI tract effects (e.g., hemorrhage and irritation) were evident in 4/11 and 6/11 dogs, respectively.

The acute inhalation toxicity of 1,2-dichloropropane has been investigated in rats, mice, guinea pigs, rabbits and dogs by Highman and Heppel (1946) and Heppel et al. (1946, 1948). Mice were more sensitive to inhaled 1,2-dichloropropane than were other species. Exposure to 400 ppm (1850 mg/m³) for 7 hours resulted in some deaths among C57 mice (Heppel et al.,

1948). Mice that died or were killed after 1 or 2 such exposures had fatty degeneration of the liver and kidneys. No significant treatment-related effects were seen among other species exposed subchronically to 400 ppm (7 hours/day, 5 days/week), and virtually no histopathologic effects were seen in rats and guinea pigs killed after a few exposures (Heppel et al., 1948).

At 10,400 mg/m³ (~2200 ppm) for 7 hours, all exposed mice died; histopathologic examinations were not performed. Even at 4400 mg/m³ (~1000 ppm), all exposed mice died by 4 hours of exposure; histopathologic changes included fatty degeneration of the liver and kidneys (Heppel et al., 1946). Histopathologic effects were observed in the livers and kidneys of rats, guinea pigs and rabbits and in the adrenals of rats and guinea pigs following one or a few 7-hour exposures to 2200 ppm (~10,400 mg/m³) of 1,2-dichloropropane (Heppel et al., 1946; Highman and Heppel, 1946). A few deaths occurred among the rats and rabbits. A more recent acute inhalation study (Drew et al., 1978) in rats provided evidence of liver damage in rats exposed to 1000 ppm (~4630 mg/m³); SGOT, SGPT and OCT activities were increased.

The acute oral toxicity studies do not clearly define a NOEL or NOAEL for exposure to 1,2-dichloropropane. Mortality data from single-dose oral studies reported in the draft report (NTP, 1983 draft) indicate that mice are more sensitive to 1,2-dichloropropane than are other species. In the report (NTP, 1983 draft), an oral dose of 250 mg/kg bw/day had produced red renal medullae in 1 of 5 female mice in a 14-day study. The toxicological significance of this finding is unclear, as it was not investigated histologically.

The effect of 1,2-dichloropropane on the functional state of the liver in rats has been studied and reported in an abstract by Kurysheva and Ekshtat (1975). The groups of animals were given a daily dose of 14.4 mg/kg or 360 mg/kg of 1,2-dichloropropane orally for 30 days. The investigators reported that the levels of serum cholesterol, β-lipoprotein and γ-globulin increased after the 10th day following the daily administration of dosages. By the 20th day of dosing, the serum cholinesterase was inhibited, whereas the fructose-1-monophosphate aldolase, SGPT and SGOT enzyme activity was increased; after 30 days of dosing, SGPT was inhibited. Other information such as strain, number of animals, weight and age, as well as which doses caused which effects were not reported.

In another ingestion study in animals, Ekshtat et al. (1975), have reported the results of orally administered 1,2-dichloropropane in rats. The animals were given a daily dose of 8.8, 44 or 220 mg/kg of 1,2-dichloropropane for 20 days. The investigators observed disturbances in the animals' protein formation, hepatic enzyme levels and lipid metabolism.

The only subchronic oral study available is the gavage study by the NTP (1983 draft), in which 10 male and 10 female F344 rats were administered 0, 60, 125, 250, 500 or 1000 mg/kg bw/day and 10 male and 10 female B6C3F$_1$ mice were administered 0, 30, 60, 125, 250 or 500 mg 1,2-dichloropropane/kg bw/day in corn oil by gavage (5 days/week) for 13 weeks. Observations included mortality, body weight, overt signs of toxicity and gross appearance of organs at necropsy. Animals in the 0, 500 and 1000 mg/kg groups were also examined histopathologically. In rats, the only treatment-related

effects noted were mortality (20/20) with histopathologic effects in the livers of some but not all of the animals given 1000 mg/kg. Mortality also occurred in 5/10 male rats and 0/10 of the female rats with reduced mean terminal body weight in males in the 500 mg/kg group. In mice, 1 male from the 60 mg/kg group and 1 female from the 500 mg/kg group died. It is unclear whether these deaths were treatment-related and no other adverse effects were noted.

Only one chronic study has been performed. This study, NTP (1983 draft), was designed primarily to investigate carcinogenic effects, but also provides some information on systemic toxicity. Groups of 50 female F344 rats and 50 male and 50 female B6C3F$_1$ mice were administered 1,2-dichloropropane at 0, 125 or 250 mg/kg bw/day in corn oil by gavage (5 days/week) for ~2 years (103 weeks) (NTP, 1983 draft). Groups of 50 male F344 rats were administered 1,2-dichloropropane at 0, 62 or 125 mg/kg bw/day in the same manner. Observations included survival, body weight, overt signs of toxicity, and gross and histological appearance of a wide range of organs and tissues. In rats, survival was decreased only among the females of the 250 mg/kg group. An increased incidence of liver lesions (foci of clear cell change and focal and centrilobular necrosis) and decreased mean body weight were also observed in this group. At the 125 mg/kg dose level, survival among rats was unaffected, but males had decreased mean body weights and females had increased incidences of mammary gland hyperplasia. No effects were observed in male rats given 62 mg/kg.

In mice, there was a decrease in survival among females receiving 125 and 250 mg/kg 1,2-dichloropropane. This decrease was statistically signif-

icant ($p<0.05$) at the higher dose. Survival of treated males was unaffected. The decreased survival of treated female mice was attributed, in part, to an increased incidence of severe infections of the reproductive tract for both low- and high-dose groups. The only other non-neoplastic effects in mice were increased incidences of liver lesions (hepatomegaly and focal and centrilobular necrosis) in males receiving 125 or 250 mg/kg.

Quantification of Noncarcinogenic Effects

The quantification of the critical effects of 1,2-dichloropropane requires consideration of the toxicity resulting from acute, subchronic and chronic exposure.

Derivation of a 1-Day HA. There are insufficient toxicological data available in the published scientific literature to derive a 1-day HA. The data resulting from acute exposure to 1,2-dichloropropane from the NTP (1983 draft) study in which 5 male and 5 female mice were administered by gavage 0, 125, 250, 500 or 1000 mg 1,2-dichloropropane/kg bw/day for 14 days came closest for 1-day HA consideration; however, the toxicological significance could not be assessed in absence of histological examination of tissues.

Derivation of 10-Day HA. Three studies in animals have been reported in the scientific literature in the form of abstract or a draft report (Kurysheva and Ekshtat, 1975; Ekshtat et al., 1975; NTP, 1983 draft). However, these studies lack some relevant toxicological data necessary in the consideration of a 10-day HA. Kurysheva and Ekshtat (1975) reported the effect of 1,2-dichloropropane on the functional state of the liver of rats. The groups of animals were given a daily dose of 14.4 mg or 360 mg/kg of

1,2-dichloropropane orally for 30 days. The increase in the serum levels of serum cholesterol, lipoprotein, and gamma-globulin was noted after the 10th day following the daily administration of dosages. By the 20th day of dosing, the serum cholinesterase was inhibited, whereas the fructose-1-monophosphate aldolase, SGPT and SGOT enzyme activity was increased; after 30 days of dosing, SGPT was inhibited. Other information such as strain, number of animals, weight and age, as well as which doses caused what effects were not reported.

In another investigation study in animals, the Russian investigator Ekshtat et al. (1975) reported the results of orally administered 1,2-dichloropropane at dose levels of 8.8, 44 or 220 mg/kg for 20 days. The investigators observed disturbances in the animals' protein formation, hepatic enzyme levels and lipid metabolism. The NAS (1979) in a request from the Office of Drinking Water provided a 7-day level of 1,2-dichloropropane based on Ekshtat et al. (1975) study in rats. The following formula was used to derive a 7-day level for a 70 kg man consuming 2 ℓ water/day.

$$\frac{8.8 \text{ mg/kg/day} \times 70 \text{ kg}}{1000 \times 2 \text{ ℓ}} = 0.3 \text{ mg/ℓ for a 70 kg adult}$$

where:

8.8 mg/kg/day = minimal effect level from the subacute ingestion studies in rats

70 kg = average weight of an adult

1000 = uncertainty factor because the data are limited and incomplete

2 ℓ = water consumption/day

In the case of a 10 kg child, the level of 1,2-dichloropropane would be:

$$\frac{8.8 \text{ mg/kg/day} \times 10 \text{ kg}}{1000 \times 1 \text{ ℓ}} = 0.088 = 0.09 \text{ mg/ℓ for a 10 kg child}$$

If the NAS (1979) recommended level of 0.3 for a 70 kg adult is acceptable for a 7-day exposure of 1,2-dichloropropane, this guidance could also be considered for a 10-day HA.

The results of a subchronic oral study in rats and mice by the NTP (1983) are reported in the form of draft reports. In this study, 10 male and 10 female F344 rats were administered 0, 60, 125, 250, 500 or 1000 mg/kg bw/day and 10 male and 10 female B6C3F$_1$ mice were given 0, 30, 60, 125, 250, 500 mg/kg bw/day of 1,2-dichloropropane in corn oil gavage for 13 weeks. Observations included mortality, body weight, overt signs of toxicity and gross appearance of organs at necropsy. Animals in the 0, 500 and 1000 mg/kg groups were examined histopathologically. In rats, the treatment-related effects were mortality of all 20 rats and histopathologic effects in the livers of some of the animals at 1000 mg/kg, and mortality in males (5/10) and females (0/10) and reduced mean terminal body weight in males at 500 mg/kg. In mice, 1 male from the 60 mg/kg group and 1 female from the 500 mg/kg group died. It is unclear whether these deaths were treatment related.

In view of the inadequacy of toxicological data specified in the above studies as well as the status of the NTP report (1983) being only a "draft" at this stage, it would be prudent not to derive HAs at this time. Alternatively, one may choose in the interim period, the NAS (1979) response provided to the Office of Drinking Water, namely, 0.3 mg/ℓ for a 70 kg adult for a 7-day exposure period.

Derivation of AADI. Only one chronic ingestion study has been carried out. This study by the NTP (1983 draft), was designed primarily to investigate carcinogenic effects; it also provides some data on nontumor pathology which may be considered for a long-term ADI in absence of other chronic animal studies. However, it should be noted that the NTP report (1983) is in "draft" form and it is undergoing audit before the final report is issued. In this study, male rats were administered by gavage 0, 62 and 125 mg 1,2-dichloropropane in coin oil on 5 days/week for 103 weeks (TWA doses = 0, 44.3 or 89.3 mg/kg/day). Extensive histologic examinations were performed on some organs and tissues. A LOAEL of 62 mg/kg (44.3 mg/kg/day) was identified in this study for male rats. At this dose level, mean body weight was 5% lower than controls, but was considered by the NTP (1983 draft) to be comparable to that of controls.

Carcinogenic Effects

The chronic gavage study by the NTP (1983 draft) is the only adequately designed carcinogenicity study available. Groups of 50 female F344 rats and 50 B6C3F_1 mice of each sex were gavaged with 0, 125 or 250 mg/kg bw/day of 1,2-dichloropropane (in corn oil) on 5 days/week for 103 weeks. Groups of 50 male F344 rats were treated in the same manner, but with 0, 62 or 125 mg/kg bw/day. Survivors were killed at 105-108 weeks (rats) and 105-107 weeks (mice). The results suggest that 1,2-dichloropropane was carcinogenic for male and female B6C3F_1 mice, as indicated by dose-related increased incidences of hepatocellular adenomas in males [control, 7/50; low-dose, 10/49; high-dose, 16/50 (p=0.03)] and in females [control 0/50; low-dose, 4/50; high-dose, 5/50 (p=0.03)]. In addition, the incidences of hepatocellular carcinomas were increased numerically in males (control, 11/50;

low-dose, 16/49; high-dose, 16/50) and in females (control, 1/50; low-dose, 3/50; high-dose, 4/50), although these increases were not statistically significant. The combined incidences of hepatocellular adenoma or carcinoma in male and female mice were also statistically significantly increased above control incidences (see Table V-3 in Chapter V and the Quantification of Carcinogenic Effects Section in this Chapter). The data for liver tumor incidences in the vehicle controls were essentially equal to historical control data according to the NTP (1983 draft).

Evidence of carcinogenicity in rats was equivocal. In female rats, a significant, dose-related increase in mammary gland adenocarcinomas (control, 1/50; low-dose, 2/50; high-dose, 5/50) was found after adjustment for intercurrent mortality. Survival in the high-dose group was markedly reduced, and the majority of mammary adenocarcinomas were found in animals killed at the end of the study (control, 1/37; low-dose, 2/43; high-dose, 4/16). It was noted that this tumor type is relatively uncommon in female F344 rats (see the Carcinogenicity Section in Chapter V). 1,2-Dichloropropane did not appear to be carcinogenic to male F344 rats in this study.

The only other study of carcinogenic potential of 1,2-dichloropropane was an inhalation study by Heppel et al. (1948), in which 80 C3H mice were exposed to 400 ppm (~1850 mg/m^3) 1,2-dichloropropane for 4-7 hours/day, 5 days/week for up to 37 exposures and followed by an observation period of 7 months. Most of the mice died during the exposure period. Only three mice survived to the end of the observation period; all three had multiple hepatomas. Because of the high mortality and inadequate reporting of data, these results do not lend themselves to further interpretation.

1,2-Dichloropropane has been tested for mutagenicity in a variety of *in vitro* systems. In the reverse mutation assay with *S. typhimurium*, 1,2-dichloropropane exhibited positive activity in strains TA1535 and TA100 (DeLorenzo et al., 1977; Stolzenberg and Hine, 1980; Carere and Morpurgo, 1981; Principe et al., 1981). The NTP (1983 draft) obtained negative results for 1,2-dichloropropane in this assay. In the forward mutation assay with *A. nidulans*, 1,2-dichloropropane demonstrated mutagenic activity, but negative results for forward mutation were obtained when *S. coelicolor* was employed as the test organism (Carere and Morpurgo, 1981; Principe et al., 1981). In assays with Chinese hamster ovary cells, 1,2-dichloropropane demonstrated positive activity in the SCE assay and in the test for chromosome aberrations, both with and without metabolic activation (NTP, 1983 draft).

The evidence for the carcinogenicity of 1,2-dichloropropane to animals (NTP, 1983 draft), when considered together with the evidence of its mutagenicity and the known carcinogenicity of related compounds (i.e., short-chain halogenated hydrocarbons), indicates that 1,2-dichloropropane may be a carcinogen.

Quantification of Carcinogenic Effects

The dose-response data for hepatocellular adenoma and carcinoma in $B6C3F_1$ mice (NTP, 1983 draft), shown in Table VIII-1, can be used for quantitative assessment of cancer risk from exposure to 1,2-dichloropropane. Based on these data and using a linearized multistage model adopted by the U.S. EPA (45 FR 79318), a carcinogenic potency factor (q_1^*) for humans of

TABLE VIII-1

Data Used for the Derivation of q_1^*[a]

Compound: 1,2-Dichloropropane

Species, Strain, Sex: mice, $B6C3F_1$, male and female

Body Weight: males 0.04 kg, females 0.038 kg (measured)

Length of Exposure (l_e) = 721 days

Length of Experiment (L_e) = 742 days

Lifespan of Animal (L) = 742 days

Tumor Site and Type: liver/adenoma or carcinoma

Route, Vehicle: by gavage/corn oil

Experimental Doses or Exposures (mg/kg/day, 5 days/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested (or Examined)[b]	
		males	females
0	0	18/50 (p=0.003)	1/50 (p=0.009)
125	86.8	25/49	7/50 (p=0.030)
250	173.5	32/50 (p=0.004)	9/50 (p=0.008)

Human $q_1^* = 6.33 \times 10^{-2}$ $(mg/kg/day)^{-1}$ from the data for male mice
Human $q_1^* = 2.25 \times 10^{-2}$ $(mg/kg/day)^{-1}$ from the data for female mice

[a]Source: NTP, 1983 draft

[b]Probability values for the Cochrane-Armitage test for linear trend are given after the incidence of tumors in controls and for the Fisher exact test are given after the incidence of tumors in dosed groups, when $p<0.05$.

6.33×10^{-2} $(mg/kg/day)^{-1}$ was calculated from the data for male mice and a q_1^* of 2.25×10^{-2} $(mg/kg/day)^{-1}$ was calculated from the data for female mice. The higher of the two values is the appropriate basis for the estimation of cancer risk levels. The doses corresponding to increased lifetime cancer risks for a 70 kg man of 10^{-4}, 10^{-5} and 10^{-6} are 1.11×10^{-1}, 1.11×10^{-2} and 1.11×10^{-3} mg/day, respectively. Assuming a water consumption of 2 ℓ/day, the corresponding concentrations of 1,2-dichloropropane in water are $\sim 5.6 \times 10^{-2}$, 5.6×10^{-3} and 5.6×10^{-4} mg/ℓ, respectively. Other cancer based criteria could not be located in the available literature. However, it should be pointed out that these risk assessments for 1,2-dichloropropane are based on the results of carcinogenicity bioassay in animals reported in the NTP (1983 draft) report and may change pending audit of the experimental data and issuance of a final report by the NTP.

Special Considerations

Synergistic Effects. Drew et al. (1978) studied the effects of 1,2-dichloropropane in combination with trichloropropane on rat serum enzymes. Male CD-1 rats were exposed by inhalation to a mixture of 1000 ppm (4621.7 mg/m³) 1,2-dichloropropane and 500 ppm (2310.8 mg/m³) trichloropropane for 4 hours. Levels of SGOT, SGPT, glucose-6-phosphatase and OCT were measured 24 and 48 hours after a single exposure to the mixture. An initial depression in the level of glucose-6-phosphatase was observed on the day of exposure and within the first 24 hours. SGOT, SGPT and OCT were all increased after exposure to the mixture. According to the authors, the compounds had an additive effect for SGOT and OCT at 24 hours. The only greater-than-additive (synergistic) effect was observed for SGPT at 24 hours; however, this effect decreased by 48 hours and was significantly

less-than-additive (antagonistic) for SGOT, SGPT and OCT by 48 hours. Thus, results of this study suggested that 1,2-dichloropropane and trichloropropane did not act in a synergistic manner with respect to the levels of serum enzymes in the rat.

High Risk Subpopulations. Human data that would establish the existence of sensitive subpopulations were not found in the literature searched. Data from animal studies suggest considerable inter- and intraspecies differences in susceptibility (see the Noncarcinogenic Effects Section). In addition, individuals who are exposed occupationally to 1,2-dichloropropane (e.g., agricultural workers and those involved in the manufacture of the chemical) may be at somewhat greater risk because of their additional exposure.

Summary

The data base for the toxicity of 1,2-dichloropropane is limited, consisting of a number of studies from the older literature and the NTP (1983 draft) carcinogenicity study. (Note: A final NTP report is in preparation.)

The data base for the toxicity of 1,2-dichloropropane is limited, consisting of a number of studies from the older literature and a draft of an NTP carcinogenicity study. The recommended criteria are summarized in Table VIII-2. Note, however, that the 1-day and 10-day HAs and the AADI are not recommended due to the inadequacy of available toxicological studies.

Based on the heptatocellular adenoma and carcinoma response of male mice given 1,2-dichloropropane by gavage (NTP, 1983 draft), an excess lifetime

TABLE VIII-2

Criteria for 1,2-Dichloropropane

Criteria	mg/ℓ	mg/kg bw/day
1-day HA (adult)	insufficient data	--
1-day HA (child)	insufficient data	--
10-day HA (adult)	insufficient data	--
10-day HA (child)	insufficient data	--
Lifetime AADI	insufficient data	--
10^{-4} Excess Cancer Risk*	5.6×10^{-2}	1.6×10^{-3}
10^{-5} Excess Cancer Risk*	5.6×10^{-3}	1.6×10^{-4}
10^{-6} Excess Cancer Risk*	5.6×10^{-4}	1.6×10^{-5}

*Based on the NTP (1983 draft) report; subject to change following availability of the final report.

cancer risk at 10^{-4}, 10^{-5} and 10^{-6} associated with water concentration would be 5.6×10^{-2}, 5.6×10^{-3} or 5.6×10^{-4} mg/ℓ, respectively. It should be pointed out that these risk estimates are based on the results of the NTP (1983 draft) report and subject to change following the audit of the experimental data and issuance of the final report by the NTP.

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